MEDICAL SCHOOL
LIBRARY

EX LIBRIS

Medical Library Exchange

Columbia University Medical
Library.

4

Digitized by the Internet Archive
in 2007 with funding from
Microsoft Corporation

UNIVERSITY
LIBRARY

A TEXT-BOOK
of
PHYSIOLOGY

For
STUDENTS AND PRACTITIONERS OF MEDICINE

By
RUSSELL BURTON-OPITZ

S. M., M. D., PH. D.

Associate Professor of Physiology, Columbia University; Professorial
Lecturer in Physiology in Teachers College and the
Extension Department of Columbia University

QP34
B967
1920

ILLUSTRATED

UNIVERSITY OF CALIFORNIA
LIBRARY

PHILADELPHIA AND LONDON

W. B. SAUNDERS COMPANY

1921

R

49342

154-5311
154-5311
154-5311

A TEXT BOOK

PHYSIOLOGY

OF THE HUMAN BODY

Copyright, 1920 by W. B. Saunders Company

Reprinted November, 1920

Reprinted July, 1921

THE W. B. SAUNDERS COMPANY

PHILADELPHIA

PRINTED IN AMERICA

PRESS OF

W. B. SAUNDERS COMPANY
PHILADELPHIA

B967
1920

PREFACE

IN this book is embodied in large part the subject matter of a series of lectures which it has been my privilege to deliver annually to the students of the College of Physicians and Surgeons of Columbia University. Fully realizing that the medical student is pressed for time and is imbued with a definite desire to apply his physiological knowledge in a practical way at the bedside, it has been my endeavor to invade the field of Comparative Physiology no farther than is absolutely necessary to form a thorough basis for the physiological problems which are of special importance to medical men. For this reason, I have usually allowed the different discussions to be preceded by brief remarks of a more general character, hoping thereby to retain a happy medium between Special Physiology and Comparative Physiology.

The same principle I have followed with regard to Physics and Chemistry. While the medical student of the present day has been required to pass a certain number of courses in these subjects preliminary to the study of medicine, I realize that time stimulates forgetfulness, and that he may not have been in a particularly favorable position during his years at College to grasp the practical bearing of many of the topics then dealt with. For this reason, I have thought it advantageous to him, as well as to myself as a teacher, briefly to review those physical and chemical principles which are more directly related to the subject matter of Physiology. The same course I have followed pertaining to Histology.

Together with Anatomy, and often with an unmistakable attitude of charity, Physiology has been regarded as one of the foundation stones of modern medicine. It seems to me, however, that this milestone has been passed some time ago, and that the sole hope of modern medicine is Physiology, or in a larger sense, the experimental sciences. Since it may, therefore, be contended that "Medicine is Physiology," the student should make a conscientious effort to become thoroughly acquainted with this subject. It is by no means an easy task that lies before him, but having fulfilled this duty, the reward is large, because no other science is quite so interesting as Physiology, and no other combines theory and practice so happily. I venture to hope that this book will help him in this attempt, in spite of its doubtlessly many shortcomings, for which I beg his generous indulgence.

Inasmuch as the subject of Physiology is altogether too large to be dealt with in detail within the space of an ordinary text-book, brevity and the elimination of everything that may be considered of

minor importance, are essential. The material gained in the course of this process of elimination, merits no further abridgment and the student should acquire a thorough working knowledge of it. In recent years our physiological literature has been enriched by a number of very admirable text-books upon physiological chemistry, such as those of Hammarsten, Mathews, Meleod, Bayliss, Oppenheimer, Lusk, Rubner, and Gautier. I am deeply sensible of my obligations to these authors for the material I have gathered from their writings. But, since this field has been so minutely covered by them, I have not attempted in the present book to give anything further than a general story of these events. The student should be in possession of at least one of these treatises as a means of gathering his chemical knowledge from a more thorough and detailed source than I could possibly present. It has been my endeavor to remain as much as possible on the mechanical or physical side of Physiology without, however, completely eliminating its chemical aspect. It is certainly my ardent desire to keep Biological Chemistry within the fold of Physiology in a relationship most beneficial to both sciences.

Being convinced that diagrams and simple sketches are of inestimable value to the student, I have inserted in the present book a large number of them. Some of these may lay claim to a certain originality, while others are mere modifications of earlier sketches of a similar kind. For the latter I am indebted to the authors and publishers of Quain's Anatomy, Herrick's "Elements of Neurology," Schäfer's "Essentials of Histology," Starling's "Human Physiology," and Howell's "Text-book of Physiology." I am also very glad to acknowledge my obligation to the publishers of Verworn's "Allgemeine Physiologie," Winterstein's "Handbuch der vergleichenden Physiologie," Nagel's "Handbuch der Physiologie," Luciani's "Fisiologia Humana," and Oppenheimer's "Handbuch der Biochemie." The chemical subject matter of this book has been kept in close conformity to this standard work, while the introductory remarks pertaining to the structural and functional aspects of the cell, have been closely allied to the well-known treatises of Wilson and Verworn.

R. BURTON-OPITZ.

COLUMBIA UNIVERSITY,
NEW YORK CITY;

CONTENTS

PART I

THE PHYSIOLOGY OF MUSCLE AND NERVE

SECTION I

GENERAL PHYSIOLOGY

CHAPTER I

	PAGE
LIVING SUBSTANCE	17

CHAPTER II

GENERAL PHENOMENA OF LIFE	29
-------------------------------------	----

SECTION II

THE PHYSIOLOGY OF MUSCLE AND NERVE

CHAPTER III

MOTION	36
------------------	----

CHAPTER IV

THE GRAPHIC REGISTRATION OF MUSCULAR CONTRACTION. METHODS OF STIMULATION OF MUSCLE AND NERVE	53
---	----

CHAPTER V

PECULIARITIES OF MUSCLE TISSUE	65
--	----

CHAPTER VI

THE CHARACTER OF THE CONTRACTION OF MUSCLE.	70
---	----

CHAPTER VII

THE FACTORS VARYING THE CHARACTER OF THE CONTRACTION	76
--	----

CHAPTER VIII

THE CHARACTER OF THE CONTRACTION OF SMOOTH MUSCLE.	83
--	----

CHAPTER IX

THE CHEMISTRY OF MUSCLE	85
-----------------------------------	----

CHAPTER X

THE PRODUCTION OF ENERGY IN MUSCLE	93
--	----

SECTION III

THE PHYSIOLOGY OF NERVE

CHAPTER XI

	PAGE
THE NEURON AND ITS CONDUCTING PATHS	108

CHAPTER XII

THE PHENOMENA OF CONDUCTION IN NERVE.	124
---	-----

CHAPTER XIII

THE REACTION OF NORMAL AND ABNORMAL NERVE AND MUSCLE TO THE CONSTANT AND INTERRUPTED ELECTRICAL CURRENTS	142
--	-----

PART II

THE BLOOD AND LYMPH. IMMUNITY

SECTION IV

THE BLOOD

CHAPTER XIV

GENERAL CHARACTERISTICS OF THE BLOOD.	157
---	-----

CHAPTER XV

THE CHEMICAL COMPOSITION OF THE BLOOD.	168
--	-----

CHAPTER XVI

THE RED BLOOD CORPUSCLES	172
------------------------------------	-----

CHAPTER XVII

THE WHITE BLOOD CORPUSCLES	199
--------------------------------------	-----

CHAPTER XVIII

THE BLOOD PLATELETS	207
-------------------------------	-----

CHAPTER XIX

THE COAGULATION OF THE BLOOD	211
--	-----

CHAPTER XX

THE TOTAL QUANTITY AND DISTRIBUTION OF THE BLOOD—LOSS OF BLOOD.	226
---	-----

SECTION V

THE LYMPH

CHAPTER XXI

	Page
PROPERTIES AND FORMATION OF LYMPH	233

SECTION VI

RESISTANCE AND IMMUNITY

CHAPTER XXII

THE BLOOD AND LYMPH AS PROTECTIVE MECHANISMS	245
--	-----

PART III

THE CIRCULATION OF THE BLOOD

SECTION VII

THE MECHANICS OF THE HEART

CHAPTER XXIII

A COMPARATIVE STUDY OF THE CIRCULATORY SYSTEM	253
---	-----

CHAPTER XXIV

THE ARRANGEMENT OF THE MUSCULATURE OF THE HEART	263
---	-----

CHAPTER XXV

THE CARDIAC CYCLE (REVOLUTIO CORDIS)	272
--	-----

CHAPTER XXVI

THE PHENOMENA NOTED DURING EACH CARDIAC CYCLE	280
---	-----

SECTION VIII

THE NERVOUS REGULATION OF THE HEART

CHAPTER XXVII

CARDIAC INHIBITION AND ACCELERATION	309
---	-----

SECTION IX

FUNCTIONAL PECULIARITIES OF THE CARDIAC MUSCLE TISSUE

CHAPTER XXVIII

THE ORIGIN OF THE HEART BEAT	331
--	-----

CHAPTER XXIX

	PAGE
THE PHYSIOLOGICAL PROPERTIES OF CARDIAC MUSCLE	338

SECTION X

THE MECHANICS OF THE CIRCULATION—
HEMODYNAMICS

CHAPTER XXX

PHYSICAL CONSIDERATION	347
----------------------------------	-----

CHAPTER XXXI

BLOOD PRESSURE	354
--------------------------	-----

CHAPTER XXXII

THE PULSATORY VARIATIONS IN BLOOD PRESSURE	377
--	-----

CHAPTER XXXIII

THE BLOOD FLOW.	394
-------------------------	-----

SECTION XI

THE NERVOUS REGULATION OF THE BLOOD-VESSELS

CHAPTER XXXIV

THE INNERVATION OF THE BLOOD-VESSELS OF DIFFERENT ORGANS.	411
---	-----

CHAPTER XXXV

THE CIRCULATION THROUGH SPECIAL ORGANS	427
--	-----

PART IV

RESPIRATION, VOICE AND SPEECH

SECTION XII

RESPIRATION

CHAPTER XXXVI

THE STRUCTURE AND FUNCTION OF THE ELEMENTARY LUNG	445
---	-----

CHAPTER XXXVII

THE MECHANICS OF THE RESPIRATORY MOVEMENTS	454
--	-----

CHAPTER XXXVIII

THE FREQUENCY AND CHARACTER OF THE RESPIRATORY MOVEMENTS	472
--	-----

CHAPTER XXXIX

	PAGE
THE CHEMISTRY OF RESPIRATION	486

CHAPTER XL

THE SEAT AND NATURE OF THE OXIDATIONS.	508
--	-----

CHAPTER XLI

THE RESPIRATORY INTERCHANGE UNDER DIFFERENT CONDITIONS	514
--	-----

CHAPTER XLII

THE NERVOUS REGULATION OF RESPIRATION.	528
--	-----

SECTION XIII

VOICE AND SPEECH

CHAPTER XLIII

THE GENERAL ARRANGEMENT OF THE PHONATING ORGANS	540
---	-----

CHAPTER XLIV

PHONATION	549
---------------------	-----

PART V

THE CENTRAL NERVOUS SYSTEM

SECTION XIV

THE FUNCTIONAL SIGNIFICANCE OF THE NERVOUS SYSTEM	
---	--

CHAPTER XLV

THE STRUCTURAL ARRANGEMENT OF THE NERVOUS SYSTEM	557
--	-----

CHAPTER XLVI

THE FUNCTIONAL ARRANGEMENT OF THE NERVOUS SYSTEM	565
--	-----

CHAPTER XLVII

THE FUNCTIONAL UNIT OF THE NERVOUS SYSTEM	574
---	-----

CHAPTER XLVIII

REFLEX ACTION.	583
------------------------	-----

SECTION XV

THE FUNCTIONS OF THE SPINAL CORD

CHAPTER XLIX

THE SPINAL CORD AS A REFLEX CENTER—ITS POWER OF AUTOMATICITY.	PAGE 594
---	-------------

CHAPTER L

THE SPINAL CORD AS A CONDUCTING PATH. ITS TROPHIC FUNCTION.	603
---	-----

SECTION XVI

THE AUTONOMIC NERVOUS SYSTEM

CHAPTER LI

THE SYMPATHETIC AND PARASYMPATHETIC SYSTEMS.	627
--	-----

SECTION XVII

THE MEDULLA OBLONGATA AND THE CRANIAL NERVES

CHAPTER LII

THE FUNCTION OF THE MEDULLA OBLONGATA	640
---	-----

CHAPTER LIII

THE CRANIAL NERVES.	642
-----------------------------	-----

SECTION XVIII

THE CEREBRUM

CHAPTER LIV

THE GENERAL FUNCTION OF THE CEREBRUM.	657
---	-----

CHAPTER LV

CEREBRAL LOCALIZATION	671
---------------------------------	-----

CHAPTER LVI

CEREBRAL LOCALIZATION (<i>Continued</i>)	681
--	-----

SECTION XIX

THE CEREBELLUM. THE PROTECTIVE MECHANISM OF THE NERVOUS SYSTEM

CHAPTER LVII

THE CEREBELLUM	706
--------------------------	-----

CHAPTER LVIII

	PAGE
THE PROTECTIVE MECHANISMS OF THE NERVOUS SYSTEM	716

PART VI

THE SENSE-ORGANS

SECTION XX

SPECIAL SOMATIC AND VISCERAL RECEPTORS

CHAPTER LIX

CLASSIFICATION OF THE SENSE-ORGANS	727
--	-----

CHAPTER LX

THE SENSES OF PRESSURE OR TOUCH, PAIN, AND TEMPERATURE.	734
---	-----

CHAPTER LXI

THE SENSES OF SMELL, TASTE, HUNGER AND THIRST.	743
--	-----

SECTION XXI

THE SENSE OF HEARING

CHAPTER LXII

THE CAUSE AND CHARACTER OF THE SOUND WAVES	756
--	-----

CHAPTER LXIII

THE EXTERNAL AND MIDDLE PORTIONS OF THE EAR	763
---	-----

CHAPTER LXIV

THE INTERNAL EAR OR LABYRINTH	771
---	-----

SECTION XXII

THE SENSE OF EQUILIBRIUM

CHAPTER LXV

THE SENSE OF POSITION. STATIC SENSE	781
---	-----

CHAPTER LXVI

THE SENSE OF MOVEMENT—DYNAMIC SENSE	785
---	-----

SECTION XXIII

THE SENSE OF SIGHT

CHAPTER LXVII

	PAGE
PHYSIOLOGICAL OPTICS	794

CHAPTER LXVIII

THE GLOBE OF THE EYE AND ITS PROTECTIVE APPENDAGES.	803
---	-----

CHAPTER LXIX

THE CORNEA, IRIS AND AQUEOUS HUMOR	809
--	-----

CHAPTER LXX

THE CILIARY BODY AND LENS	819
-------------------------------------	-----

CHAPTER LXXI

THE RETINA	831
----------------------	-----

CHAPTER LXXII

THE FORMATION OF THE IMAGE UPON THE RETINA	846
--	-----

CHAPTER LXXIII

ABNORMALITIES IN THE REFRACTION OF THE EYE	853
--	-----

CHAPTER LXXIV

BINOCULAR VISION	869
----------------------------	-----

CHAPTER LXXV

COLOR VISION	879
------------------------	-----

PART VII

SECRETION

SECTION XXIV

THE EXTERNAL SECRETIONS

CHAPTER LXXVI

THE GROUP OF THE CUTANEOUS SECRETIONS	891
---	-----

CHAPTER LXXVII

THE LYMPHATIC AND MUCOUS SECRETIONS	903
---	-----

CHAPTER LXXXVIII

PAGE

THE DIGESTIVE SECRETIONS	908
------------------------------------	-----

CHAPTER LXXIX

THE DIGESTIVE SECRETIONS (<i>Continued</i>).	918
--	-----

CHAPTER LXXX

THE DIGESTIVE SECRETIONS (<i>Continued</i>).	938
--	-----

SECTION XXV

THE INTERNAL SECRETIONS

CHAPTER LXXXI

THE THYROID AND PARATHYROID BODIES. THE THYMUS, LIVER, AND PAN- CREAS	951
--	-----

CHAPTER LXXXII

THE ADRENAL BODIES, HYPOPHYSIS, PINEAL GLAND, TESTES AND OVARIES. .	967
---	-----

PART VIII

METABOLISM

SECTION XXVI

DIGESTION

CHAPTER LXXXIII

THE CHEMISTRY OF DIGESTION	985
--------------------------------------	-----

CHAPTER LXXXIV

THE MECHANICS OF DIGESTION.	998
-------------------------------------	-----

SECTION XXVII

ABSORPTION

CHAPTER LXXXV

THE ABSORPTION OF THE REDUCED FOODSTUFFS FROM THE ALIMENTARY CANAL	1022
---	------

CHAPTER LXXXVI

THE HISTORY OF THE DIFFERENT FOODSTUFFS IN THE BODY.	1037
--	------

CHAPTER LXXXVII

	PAGE
THE METABOLIC REQUIREMENTS OF THE BODY	1052

CHAPTER LXXXVIII

THE NUTRITIVE VALUE OF FOOD	1058
---------------------------------------	------

SECTION XXVIII

EXCRETION

CHAPTER LXXXIX

THE SECRETION OF URINE	1064
----------------------------------	------

CHAPTER XC

THE EXPULSION OF THE URINE. MICTURITION	1075
---	------

CHAPTER XCI

THE COMPOSITION OF THE URINE	1080
--	------

SECTION XXIX

ANIMAL HEAT

CHAPTER XCII

THE PRODUCTION AND DISSIPATION OF HEAT	1089
--	------

PART IX

REPRODUCTION

SECTION XXX

THE REPRODUCTIVE ORGANS

CHAPTER XCIII

GROWTH, REGENERATION AND REPRODUCTION	1109
---	------

CHAPTER XCIV

THE MALE AND FEMALE REPRODUCTIVE ORGANS	1122
---	------

CHAPTER XCV

THE DEVELOPMENT OF THE EMBRYO	1135
---	------

INDEX.	1147
----------------	------

PART I

THE PHYSIOLOGY OF MUSCLE AND NERVE

SECTION I

GENERAL PHYSIOLOGY

CHAPTER I

LIVING SUBSTANCE

Definition and Scope of Physiology.—The science of physiology deals with the processes occurring in living matter. It is the study of the dynamics of life and as such should be extended to the entire realm of living entities, to animals as well as to plants, and to simple as well as to complex organisms. Physiology, however, deals solely with the functional aspect of living substance, its structural characteristics being taken care of by the sciences of morphology, anatomy and histology. But inasmuch as an analysis of the function of a part cannot well be attempted without a thorough understanding of its structure, it must be clear that the best results can only be obtained if these sciences are brought into the closest possible relationship. A study of the function of the eye is scarcely feasible without having obtained first of all a clear conception of the general arrangement and structural details of the tissues entering into its formation. This is also true of the ear, the heart, the brain and all other organs of our body. Physiology, therefore, presents itself as an important unit of the science of biology, which takes cognizance of all things possessing life, as follows:

The analysis of the phenomena of life also necessitates as a prerequisite an adequate knowledge of physics and chemistry. Without these sciences physiological progress would indeed be slow or even impossible. This fact accounts in a way for the almost exclusive position which anatomy has enjoyed until comparatively recent years. As the acquisition of gross structural data is not at all dependent upon the development of the supplementary sciences, anatomy has been able to advance practically without restrictions of any kind. At the close of the nineteenth century it had thus acquired an almost dominating position. On the functional side, scarcely any progress was made until the beginning of the sixteenth century, when Paracelsus (1493-1541) attacked the doctrines of Galinus (131-200) and developed a physiological system of his own. Greatly aided by the anatomical discoveries of Vesalius, Eustachius, Faloppio and Serveto, it was left to Harvey (1578-1657) to unravel the secrets of the circulation of the blood. This discovery put an end to speculative physiology and initiated experimental physiological methods. Harvey, moreover, propounded a doctrine which was destined to exert a profound influence upon the development of modern physiology, namely, his doctrine "*de generatione animalium*." In recent years this work has dominated our views regarding the origin of animal life and has led to the dictum of "*omne vivum ex ovo*."

The seventeenth century is a memorable one for physiology, because it produced a Copernicus, a Galileo, a Descartes, a Boyle and a Newton, thus furthering our knowledge of physics. Of scarcely lesser importance, however, is the construction of the compound microscope which made the histological discoveries of Leeuwenhoek (1632-1723), Malpighi (1628-1694) and Swammerdam (1637-1685) possible. Then followed Albrecht v. Haller (1708-1777) who not only greatly promoted the experimental side of physiology but also combined the data then known into a homogeneous whole and thus gave an independent existence to our Science. At about this time were made the far reaching chemical discoveries of Priestley (1773-1804), Lavoisier (1743-1794) and Girtanner (1760-1800).

The period from 1800 to about 1860 is commonly regarded as the renaissance period of physiology. It is dominated by such men as Johannes v. Müller (1801-1858) and Johannes Purkinje and, on the chemical side, by Wöhler (1800-1882)¹ and v. Liebig (1803-1873). Physiology at once began to profit by the discoveries in chemistry, because they found immediate application in the investigations of problems connected with respiration, digestion and secretion. From this time on physiology shows two tendencies, namely a physical and a chemical. Very fortunately, however, this division has re-

¹ Mention is usually made of Wöhler, because he succeeded in 1828 in producing urea synthetically. In reality, however, this synthesis was preceded by several others, namely, by that of alcohol (Hennel), that of acetic acid (Döbereiner, 1822) and that of oxalic acid (Scheele, 1776).

mained largely theoretical until more recently, although it is quite true that an expert knowledge of more than one of these fundamental sciences can scarcely be demanded of any physiologist. This new tendency soon forced physiologists to confine their constructive work either to physical or to chemical physiology. The former group of investigators includes such men as E. H. Weber (1795-1878), Volkmann (1801-1877), Ludwig (1816-1895), Helmholtz (1821-1894), Du Bois-Reymond (1818-1896), Marey (1830-1904), Bernard (1813-1878); and the latter, such men as Voit (1831-1908), Pflüger (1829-1910), Kossel (1853), Zuntz (1847), and Hofmeister (1808-1878).

Physiology, therefore, belongs essentially to the nineteenth century. It is a comparatively new science, but is unfolding itself very rapidly, so that it now forms the chief basis of modern medicine. This is the age of the experimental sciences and very rightly so, because in them lies our greatest hope of benefiting mankind. As Verworn expresses it, the struggle for existence forces man to master the forces of nature and to eradicate all those which tend to enfeeble him. Physiology constitutes a means which is used chiefly to combat the latter. Its ultimate object, therefore, is the welfare of mankind. In order to attain this end, it cannot confine itself to man and the higher animals, but must include living matter wherever found, even that forming the most primitive organisms and plants. For this reason, physiology does not always present a wholly practical aspect, but follows at times a purely scientific course of inquiry. The results of the latter, however, are not to be undervalued, because as man is not accessible to physiological methods, excepting in a few special instances, we are constantly forced to base our conclusions upon the fundamental processes displayed by the lower forms of life. That a direct comparison of this kind is permissible in most cases, has been fully demonstrated experimentally.

Animate and Inanimate Material.—Since physiology purposes to analyze the phenomena of life, it becomes necessary to familiarize ourselves with the fundamental characteristics of living substance. The layman most generally places the greatest stress upon the production of mechanical energy, such as is evinced by those apparently spontaneous movements which are made use of by living entities in changing their position in space. As a last means of differentiation between animate and inanimate bodies he employs those activities which are associated with respiration and the action of the heart. A more far-reaching differentiation, however, may be attempted upon the basis of morphological, genetic, physical and chemical peculiarities.¹ Thus, it has been said that inorganic bodies possess definite geometric proportions, and that they contain no organs and exhibit the simplest possible organization. A brief survey, however, will show that these characteristics are also presented by living substance, because organ-

¹ Verworn, *Allgemeine Physiologie*, Jena, 1909; and *Irritability*, Yale Univ. Press, 1913.

isms with mathematical contours are very numerous (radiolaria) and many of them do not exhibit a differentiation of their protoplasm nor a division of function (amœba). Upon the genetic basis, it is usually stated that organisms can only originate from organisms. But if we adhere to that theory regarding the origin of life which assumes that the first cell arose in consequence of a combination of inorganic substances at a time when conditions upon this earth permitted this union to take place,¹ this difference cannot be said to be of fundamental importance. It is conceivable that living matter appeared as a result of the evaporation of water containing the common salts. In the course of this concentration cyanides and other similar organic compounds were formed in consequence of vigorous electrical disturbances. These elementary organic globules eventually gave rise to cells and by descendance to all the organisms inhabiting this earth.² It is a well-known fact that inorganic substances are constantly made use of by plants in their production of organic material and lastly, it must be taken into account that not all organisms give rise to their like. For example, the workers of the bees and ants are sexually retrogressive and do not possess the power of reproduction.

The statement has also been made that living substance possesses the properties of irritability and contractility, while inorganic material does not. But if we observe an ordinary reaction between substances occurring in a test tube, we cannot fail to recognize that even inorganic matter is receptive and gives rise to motion. This is especially true of those substances which cause reactions of an explosive kind, such as nitroglycerin. The energy liberated by this body when stimulated, can scarcely be reproduced, and hence, with the exception of the fact that inorganic material presents an irritability and contractility of a type somewhat different from those shown by living substance, this basis does not furnish an actual means of differentiation.

If living substance is studied from the standpoint of chemistry, it is found that it contains certain organic bodies the complexity of which is not equalled in the inorganic world. Indeed, one of these groups, the proteids, forms a constant constituent of protoplasm, while no substance can be found in the inorganic world, which at all approaches the complexity of the proteid molecule. It is true, however, that even this difference must disappear as soon as a way has been found to produce these bodies artificially. There is one peculiarity, however, which is decisive and that is the specific metabolic function of living matter. Not only is it capable of altering its composition constantly, but also of giving off certain waste products which are subsequently replaced by new material. Life, therefore, is characterized by nothing more than a specific metabolism of certain substances and especially of the proteins. In a very general way, however, it is permissible to state that living substance is distinguished from life-

¹ Preger: Die Hypothesen über den Ursprung des Lebens, Berlin, 1880.

² E. Hæckel: Gen. Morph. der Organismen, Berlin, 1866.

less material, whether inorganic or organic, by its properties of irritability, conductivity, contractility, metabolism and reproduction.

The Structural Basis of Life.—While living substance appears in many forms, it always presents itself as an entity which is capable of leading an independent existence. It is living organic material and as such is generally arranged in the form of *cells*. In a general way, it may be said that this term is applied to the smallest particles of living substance still capable of existing independently of others. Hence, the cell represents the simplest type of individuality of living substance and constitutes a unit in structure as well as in function.

It is true, however, that our conception of a cell is not at all concise, because cells may exhibit very different characteristics. To begin with, the term "cell" was employed by botanists to describe those structural units which make up the stem and the leaves of plants. In a similar way it was found later on that the organs and tissues of the higher animals are not composed of homogeneous masses of living substance, but of a multitude of very small particles which are separated from one another by partitions. In both instances the cell was finally observed to be a definite unit of the entire mass, consisting of a membrane investing a semi-solid globule of protoplasm and a dark body, or nucleus.

It soon became evident that this conception was not absolutely correct, because the studies of Schultze¹ upon the structure of the rhizopods proved that there are organisms in existence which are not surrounded by a cell membrane, but appear merely as naked masses of living substance possessing the same characteristics as the viscous contents of the plant cell, or protoplasm. In accordance with this discovery, it has since been held that the essential unit of the cell is the protoplasm, *i.e.*, the cell consists merely of a globule of protoplasm which may or may not be invested by a membrane. Our original idea regarding its structure has also been modified in so far as the nucleus is no longer regarded as an essential constituent. This conception necessitated a different interpretation of the discovery of Brown² from that ordinarily given to it. It will be remembered that this investigator noted that protoplasm embraces a granule possessing the power of refracting light. This fact was greatly amplified later on by Schleiden³ and Schwann⁴ who found this granule so universally present that they considered it as a constant constituent of the cell. Häckel,⁵ however, proved subsequently that many rhizopods do not contain a nucleus. In more recent years this condition has also been shown to prevail in bacteria and fungi. It seems best, however, not to emphasize this point too strongly, because while many cells do not

¹ Archiv für Anat. und Physiol., 1861.

² Transact. of the Linnean Soc., London, 1833.

³ Müller's Archiv, 1833.

⁴ Mikr. Unters. über die Struktur und den Wachstum der Tiere and Pflanzen, 1839.

⁵ Biolog. Studien, Leipzig, 1870.

display a clearly recognizable nucleus, they nevertheless contain nuclear material which, in accordance with Bütschli,¹ appears in many cases merely as dust-like fragments scattered through the cytoplasm. At best, therefore, a cell can only be defined as a globule of protoplasm containing a certain amount of nuclear material.

The term **protoplasm** (*protos*, first; *plasma*, form) is usually employed as a synonym for living substance. Huxley, for example, speaks of it as the physical basis of life, just as the cell has been designated by Brücke² as the elementary functional unit. It should be emphasized, however, that protoplasm is not a single substance, but is composed of several. It is a definite chemical compound which, in accordance with the histologists, possesses certain staining powers and, in accordance with the physiologists, exhibits a certain behavior toward the conditions under which it is made to live. In the second place, it must be remembered that protoplasm differs somewhat in its chemical composition and physical arrangement. Thus, the protoplasm composing the muscle cell is not at all identical with that forming the cells of the liver or kidney or other organs. We know this to be true, because the reactions of these diverse types of protoplasm are not absolutely the same, but vary in accordance with their function. And besides, even a single cellular unit most commonly contains more than one kind of protoplasm, namely, the fundamental substance plus certain adjuncts which to all appearances give rise to a division of labor. Thus, it is conceivable that in single protoplasmic entities, such as are presented by ameba, stentor and other unicellular organisms, a certain portion of the substance is set aside to serve the purpose of digestion, another that of excretion and still another that of locomotion.

The Structure of the Cell.—It is evident, therefore, that living matter appears in the form of cells and that these cells may be either single free-living organisms or may be combined into colonies to form the tissues and organs of the more complex animals and plants. In either case, whether forming a unicellular entity or united with others into a multicellular organism, the cell presents certain morphological and functional characteristics. Its *form* differs greatly, and while the large majority of cells retain their shape throughout their life, a certain number of them, such as the ameba, change it constantly. It may be taken for granted, however, that their fundamental shape is round, or nearly so, and that almost any polyhedral form may be imparted to them by grouping them into tissues and organs. Moreover, while some of them may attain an unusual length, others are equipped with appendages in the form of pseudopodia, flagella and cilia. Their *size*, on the other hand, differs only within relatively narrow limits. By far the greatest number of them remain below the range of ordinary vision and very few attain dimensions that may be

¹ Über den Bander Bakterien und verw. Organismen, Leipzig, 1890.

² Sitzungsber. der Wiener Akad. der Wissensch., xlv, 1861.

expressed in millimeters. The latter are commonly observed to possess ameboid motion. Consequently, the formation of a bulky organism is possible only by the union of a multitude of relatively independent cellular elements.

As has been stated above, the term protoplasm was employed originally in a morphological sense to designate the entire mass of living substance inside the cell wall with the exception of the nucleus. At the present time, however, we know that this conception is not quite correct, because the contents of the cell are really a morphological and chemical mixture. To begin with, it may be stated that a cell consists of two parts, namely of cytoplasm and of nuclear material.

The *cytoplasm* appears as a clear homogeneous, viscous "ground-substance" in which are embedded varying numbers of formed elements.¹ At times, therefore, the watery ground substance is clearly in evidence, while at other times it is hidden by granular material. The *formed elements* of the cytoplasm embrace bodies which are absolutely essential to the life of the cell as well as bodies which must be regarded as accidental admixtures. Among the former are granules representing all stages of metabolism, namely, food material ready for assimilation and the products of the cellular processes ready for excretion. Some of the latter may first be transported to distant parts of the body to be used in connection with some other function. A very important constituent of the cytoplasm of the green plants is the so-called chloroplastic material which appears as small round or tape-shaped bodies containing an intense green pigment. It is the function of this material to assimilate the carbon dioxid so that under the energy of the rays of the sun an assimilation of starch and an evolution of oxygen may be had. A similar substance is the leukoplastic material of certain plant cells which serves to build up starch from sugars. At times the cytoplasm also contains globules of fluids, the so-called vacuoles, which may be either quiescent or exhibit rhythmic contractions. Among the accidental admixtures may be mentioned the indigestible remnants of the food, such as pieces of the shells, skeletons or capsules of the organisms which have been ingested. In fact, the cytoplasm may also give lodgment to living organisms and especially to certain parasites.

Under the low power of the microscope the ground-substance of the cytoplasm presents a perfectly homogeneous hyaline appearance; indeed, such objects as the pseudopodia of the ameba and rhizopods do not display a differentiation even when observed under high powers. In most cases, however, some kind of structure may then be made out. Thus, Remak² has shown (1844) that ganglion cells possess a fibrillar interior, while Frommann and Heitzmann have proved (1867) that the fundamental structure of protoplasm is spongy.

¹ M. Heidenhain, *Plasma und Zelle*, Jena, 1911.

² *Archiv für Anat. und Physiol.*, 1844.

Bütschli,¹ in fact, believes that it possesses a honeycomb or froth-like structure. These somewhat divergent views may be classified under the following heads:

(a) The granula theory, proposed by Altman,² holds that the granules contained in protoplasm are the essential constituent and that the fluid medium is not living substance at all.

(b) The fibrillar theory assumes that the protoplasm consists of a network or clusters of fibrils containing in its meshes a certain amount of fluid material. The fibrillar reticulum or spongework is designated by Schäfer as the spongioplasm and the more fluid and structureless portion as the hyaloplasm.

FIG. 1.—THE STRUCTURE OF PROTOPLASM.

An epidermal cell of the earthworm. (After Bütschli.)

(c) The alveolar theory, advocated by Bütschli, contends that the ground-substance of the cytoplasm stores its material as globules which gradually increase in size and become separated from one another by alveolar partitions. Microscopic formations of this kind may be produced artificially by mixing oil with potassium or cane sugar. On bringing a droplet of this oil in contact with water, molecules of the latter pass inward and split the oil droplet into innumerable smaller ones until a very delicate froth is produced. The diffusion currents resulting in this mixture, are at times so intense that movements similar to amoeboid motion may be observed.

The *nucleus* of the cell appears as a rule as an oval or round body, situated near the center of the cytoplasm and sharply differentiated from it by what is known as a nuclear membrane. Many cells, however, contain nuclei which are long drawn out or constricted so as to form band-like or bead-like chains of nuclear material, while in others the nuclear material is scattered through the cytoplasm in the form of dust-like particles. Considerable variations are also noted with regard to the relative volume of the nucleus and cytoplasm, the latter forming at times merely a narrow frame around a large centrally placed nucleus.

The nucleus consists of an enveloping membrane, a network of fibers, the nuclear matrix and nucleoli. It is believed that the spongioplasm of the cytoplasm is extended into the nucleoplasm, but on a larger scale, *i.e.*, the threads are coarser and can therefore be more easily seen. The interstices of this network are filled with nuclear sap or matrix. At the different points of crossing of the filaments, the

¹ Untersuchungen über die mikrosk. Schäume und das Protoplasma, Leipzig, 1892.

² Die Elementarorg. und ihre Beziehungen zu den Zellen, Leipzig, 1890.

chromatin, of which they are composed, appears in the form of granules. Some of these are especially conspicuous and are then called pseudonucleoli. Other masses of chromatin, the true nucleoli, are sometimes found embedded in the nuclear sap. If the cell is stained with such dyes as hematoxylin or safranin, the nucleus is made to stand out prominently against the light protoplasmic ground-substance. The nucleus, however, does not absorb the pigment very evenly, because the chromoplasmic network and nucleoli possess a much greater affinity for it than the matrix. Herein really lies the reason for saying that the cell is composed of chromatic and achromatic substances; the former combine with many dyes with great ease while the latter do not.

FIG. 2.—DIAGRAM OF A CELL. (Wilson.)

The Chemistry of the Cell.—The chemical analysis of protoplasm as practised at the present time, necessitates its destruction as a functional entity. For this reason, its composition can only be deduced from that of dead organic material. Kossel¹ divides its constituents into primary and secondary, the latter being present only in some types of cells. As an example of this kind might be mentioned the glycogen of the cells of the liver. As primary constituents are to be regarded lecithin, cholesterolin (lipoids), proteids (nucleoproteids), inorganic salts and water.

As *lipoids* must be classified all those bodies which may be extracted with ether or similar solvents.² Whether the lecithin which belongs to the class of the *phosphatides*, is actually a primary constituent of the cells is still doubtful. It is

¹ Archiv für Anat. und Physiol., 1891.

² Overton, Studien über die Narkose, Jena, 1901.

found in large amounts in sperm-cells, the eggs of fishes, nervous tissue, and the yolk of eggs, and in small amounts in striated and cardiac muscle cells. *Cerebrosides*, i.e., bodies, containing nitrogen but no phosphorus, are contained in spermatozoa and leukocytes. *Fatty acid and neutral fat*, i.e., substances containing neither nitrogen nor phosphorus, are very common constituents of cells; the nucleus, however, is said to be free from fat. Cholesterin, one of the substances belonging to this group, is a primary constituent, but nothing definite regarding its origin and condition is known. The lipoids facilitate the solubility of those substances which are otherwise scarcely soluble in water. They also play a part in hemolysis and absorption.

The *proteins* are the most constant and important constituent of the cell.¹ They occur in the cytoplasm as well as in the nucleus and belong chiefly to the class of the proteids. The nucleoproteids of the nucleus are to be sharply differentiated from the proteins of the cytoplasm, because it has not been definitely settled as yet whether these bodies are absolutely identical. "Nuclein" was first isolated by Miescher² from the nuclei of the pus-corpuseles. Somewhat later Kossel³ demonstrated that the essential constituents of this body are the purin and pyrimidin substances and not the phosphorus. That this is true may be gathered from the fact that the yolk of the unfertilized egg of birds contains no purin, while the developing eggs yield large amounts of this substance. Somewhat later Altmann⁴ succeeded in abstracting nucleic acid from different proteids. This constituent of the nucleoproteids seems to be present in rather constant quantities, while the albuminous material appears to fluctuate considerably. It is usually combined with a basic albuminous substance, forming such bodies as protamin or histon. The isolation of these components of the nucleoproteid is easily effected in most cases.

Carbohydrates are not found as free primary constituents of the cell, but are contained in the nucleic acid portion of the nucleoproteids, in glycoproteids and cerebrosides. In the cells of the liver glycogen is held as a reserve foodstuff.

Among the *inorganic substances* masked iron has been shown to exist in chromatin.⁵ Less convincing results have been obtained pertaining to phosphorus. Protoplasm, however, contains many of the commonest salts, namely, sodium, potassium, magnesium, calcium, iron (sulphates, chlorides, phosphates and carbonates), and at times also iodine, manganese, copper, zinc, barium and silicon. The proportion of these elements, however, differs in different cells; in fact, those named last should be regarded merely as accidental admixtures, because they are present only under special conditions. It should also be emphasized that these inorganic substances may occur either independently or in combination with the organic material; moreover, they should not be considered as passive constituents, because they play an important part in the production of all vital phenomena.

Water constitutes about three-fourths of living substance, the remaining portion of it being composed of inorganic and organic material. In some instances, in fact, as much as 94 per cent. of it consists of water and the common salts. For this reason, it must be evident that the specific gravity of protoplasm must show considerable variations, although it may be said that its average value is about 1.025. This value, for example, holds true absolutely in the case of paramecia which Jensen⁶ subjected to different known concentrations of potassium carbonate solutions. It is conceivable, however, that certain cells, and especially those containing calcareous admixtures, exceed this value, while others, possessing prominent vacuoles, may fall below unity and be buoyant.

¹ Kanitz, in Oppenheimer's Handb. der Biochemie, ii, 1910, 213.

² Histochem. und physiol. Arbeiten, ii, 3, Leipzig, 1900.

³ Zeitschr. für physik. Chemie, x, 1866, 248.

⁴ Archiv für Anat. und Physiol., 1889, 524.

⁵ A. B. Macallum, Ergebnisse der Physiol., vii, 1908, 552.

⁶ Pflüger's Archiv, liv, 1893, 537; also: Lillie, Journ. of Morphol., xii, 1896.

The Functional Relation of the Cytoplasm and Nucleus.—The importance of the nucleus to the cell may be shown by depriving certain parts of it of its nuclear material. Thus, Hofer,¹ divided ameba in such a manner that the nucleus came to lie in each case entirely in one of the fragments. This particular fragment regenerated very quickly into a complete cell showing a perfectly normal behavior, while the non-nucleated portions lost their power of movement and ingestion of food in the course of a few days and disintegrated. This disintegration, however, could be prevented if at least a small fragment of the nucleus was apportioned to these parts.

FIG. 3.—THE FUNCTIONAL RELATION OF THE CYTOPLASM AND NUCLEUS.

A. An ameba divided into a nucleated and non-nucleated portion. B. The same portion after an interval of eight days. (After Hofer.)

Quite similarly, it was found that denucleated rhizopods and radiolaria are able to move and to ingest nutritive particles, but that the digestion of the latter is rarely completed. Furthermore, Verworn² has shown that polystomella which possesses the power of secreting calcareous material, loses this function soon after its nucleus has been removed. Plant cells behave in a similar way. Thus, Klebs³ has proved that isolated fragments of plant protoplasm are quite unable to form a cellulose membrane, while the nucleated fragments retain this faculty. In addition, it might be mentioned that the nucleus is situated as a rule in that area of the cell in which the most active growth is taking place. This tendency is well displayed in the root-hairs of plants, in which the nuclei are retained at their very tips during the development of these appendages and are then made to

¹ Jen. Zeitschr. für Naturw., 1889.

² Pflüger's Archiv, li, 1891, 1.

³ Biol. Zentralbl., 1887.

retreat into the deeper layers. This is also true of the nuclei of many secretory glands, such as the silk glands of different lepidoptera.

The nucleus, therefore, must be regarded not only as a necessary constituent of the cell, but as its most important constructive element. To be sure, many cells, such as the erythrocytes of the mammalian blood, are capable of leading an independent existence even without a nucleus, but this example can scarcely be used as a proof against the preceding statement, because these cells are nucleated when formed and do not possess the power of regeneration. Even the bacteria form only an apparent exception, because their nuclear material is either widely disseminated through the cell in the form of dust-like granules or is already arranged as spores. Obviously,

FIG. 4.—REGENERATION OF *STENTOR ROESELII*.

A. Stentor divided into two nucleated portions; B and C newly formed organisms. (Verworn.)

therefore, the chemical and structural development of the cell depends upon the nucleus. To some extent, however, it is also true that a nucleus devoid of cytoplasm, cannot exist as an independent entity. To be sure, in many cells the protoplasmic envelope is extremely narrow and in many it does not seem to be present at all. But, the spermatozoa, to which reference is now had, are not capable of transformation nor of multiplication, their sole purpose being to unite with the ova. Verworn, moreover, has shown that the isolated nucleus of the large radiolaria does not long survive its removal from the cell.

These functional differences between the cytoplasm and the nucleus are associated with definite chemical differences. This may be inferred from the important changes which the nucleus undergoes

during the division of the cell by the process of karyokinesis as well as from its peculiar staining reactions. Thus, we find that the growth and activity of the cell is accompanied by definite variations in the size and appearance of the chromatin elements. In the egg of the shark they are small at first and stain deeply, while later on they lose their staining qualities and increase in mass. At maturity, the chromosomes again become smaller and finally break up into fine granular bodies possessing an intense affinity for nuclear dyes. Regarding the chemical differences between the nucleus and the cytoplasm, little is known. The proteins of living substance are conjugated in their nature, because the simple proteins are here combined with other complex bodies. They present, however, certain distinct differences in that those of the nucleus form the class of the nucleoproteids, while those of the cytoplasm are largely compounds of protein and lecithin. The former are characterized by their content in phosphorus and by their decomposition products of nuclein and protein. Nuclein which seems to be the chief constituent of the nuclei of cells, may be broken down into nucleic acid and protamine, the latter presenting the characteristics of a protein substance.

CHAPTER II

GENERAL PHENOMENA OF LIFE

Growth and Metabolism.—Life may be investigated in different ways. To begin with, the inquiry may be directed along chemical lines, to discover not only the material entering into the composition of living matter, but also the changes which this material undergoes in the course of the vital processes. Special emphasis should in this case be placed upon its metabolism, *i. e.*, upon the changes manifested by it during its periods of assimilation and dissimulation. In the second place, life may be investigated by physical means, at which time the question regarding the energetics of protoplasm must be most carefully considered. Living matter has been found to produce energy in the form of mechanical energy, heat, light and electricity. In the third place, it is possible to study either its gross or minute structure, *i. e.*, to pay special attention to the form in which it exists, but naturally, life does not present itself exclusively in any one of these ways, but as a homogeneous whole. These methods, therefore, are employed merely for the purpose of analyzing this process from different standpoints. One amplifies the other.

Living substance is always in activity. It grows; it secretes; it moves from place to place and naturally, all these processes require work and the production of energy which is derived from the union of its dif-

ferent constituents with oxygen. Obviously, this constant liberation of energy in its various forms, must be compensated for, *i.e.*, living substance must either generate it or obtain it from some outside source. The law of the conservation of energy, however, teaches us that energy is not created but is merely transformed from one kind into another and hence, living matter must derive it from somewhere, namely, from the medium in which it lives. Various substances are here at hand which contain stored or potential energy. When assimilated by living matter, either through its respiratory or digestive channel, these chemical bodies are converted into kinetic energy.

The *metabolism* of a cell consists in a continuous decomposition and new formation of its protoplasmic material. The former process is designated as dissimilation or catabolism, and the latter as assimilation or anabolism. It is true, however, that the metabolism is uniform only in principle, because practically every type of cell has its own peculiar work to perform and hence, a number of special varieties of metabolism are obtained. Expressed in another way, it may be said that the fundamental interchange of material between the cell and its surroundings is modified in many cases to suit particular purposes. Thus, a certain group of cells may be destined to give rise to a digestive secretion, while another furnishes chiefly contractile reactions, and so on. This specificity, however, is not so clearly marked in free-living unicellular organisms as it is in the more complex animals and plants, because the function of the former is not so diversified.

The catabolic processes occurring in a cell necessitate a constant acquisition of new material to replenish that which has been lost. It is true, however, that the manner in which this assimilation is accomplished, differs somewhat in different animals and plants. An especially tedious process is in existence in the green plants, because their protoplasm is built up from the simplest possible compounds, such as carbon dioxide, water and various inorganic salts. The animal cell, on the other hand, is constituted differently so that it can also make use of the more complex foods held in the form of organic combinations. It must be evident, however, that the former can no longer be regarded as synthetic and the latter as decomposition organisms, because the metabolism of both types of cells is dependent upon processes of dissociation and synthesis. It is true, however, that the life of the animals depends upon that of the plants, because only the latter are capable of producing carbohydrates, fats and proteids from inorganic material. These are the essentials of animal life. Animals, therefore, are the parasites of the plants. There is, however, one exception to this rule, because those plants which contain no chlorophyll, such as the fungi, must make use of organic substances in order to obtain their requirement in carbon. The fungi, however, are capable of forming nitrogen from the inorganic constituents of the soil, while animals must derive their supply of nitrogen exclusively from proteids and derivative compounds. As far as their metabolism is concerned,

the fungi and allied plants form, therefore, an intermediate group between the green plants and the animals, *i.e.*, between those entities of living substance which assimilate the carbon from carbon dioxid under the influence of the rays of the sun and those which derive their energetics from foodstuffs.

Assimilation implies that the organisms must ingest nutritive material which, after its digestion, is absorbed and utilized. The manner in which this ingestion is accomplished differs materially with the general form and behavior of the organisms. In the case of free-living and naked unicellular masses, the acquisition of the nutritive substances takes place apparently at any point of the surface by the process of engulfing, while in the more specialized organisms, it occurs in a particular place, namely at the gullet. The reduction or digestion of the food is then effected by means of enzymes contained in secretions which hydrolyze it and render it dialyzable and assimilable. But while many cells possess the power of digesting the foodstuffs themselves, many do not. The latter, therefore, require already prepared food. In the higher forms this preparation is effected by special groups of cells forming the digestive organs. For this reason, we speak of intracellular and extracellular digestion.

The phenomena of *dissimilation* are ushered in by the decomposition of the protoplasm, in consequence of which the various forms of energy are then liberated. It is necessary, however, to form the material lost anew, otherwise the catabolism might progress beyond a certain limit and endanger the life of the cell. Clearly, oxygen is a necessary factor in this reduction, at least in most organisms, but it has not been definitely settled as yet whether it forms a true anabolic product of the cell in the shape of "intramolecular" oxygen, or whether it is present in the surrounding medium in its molecular form to be made use of as such whenever required. As a result of this oxidation, the cell gives rise to a number of products which are of no further use to it and are later on gotten rid of by the process of excretion. These waste materials are of many kinds. Chief among them are those arising from carbon and hydrogen, namely carbon dioxid and water. A number of them are derived from the proteids, for example, urea, uric acid, hippuric acid, creatin, etc., which are either suspended or dissolved in water. Their complete reduction frequently requires special agents which are brought to bear upon them through the media of the excretions.

The purpose of metabolism is to keep the cells in a physiological condition, as evinced by the amount of energy liberated by them. The cell, therefore, is the seat of life. It receives certain substances and with them a definite amount of potential energy which is then transformed into kinetic energy in its various forms. Thus, cells are destined to produce work, either directly or indirectly. The green plants, for example, may be regarded very largely as potential factors, because their energy must first be produced in the presence of sunlight.

To begin with, the substances consumed by them, possess no potential energy, but light, in connection with their content in chlorophyl, gives rise to a splitting of the molecules of the carbon dioxid and water so that the resulting atoms of carbon, hydrogen and oxygen are at liberty to enter other chemical combinations. In this way, a number of complex substances are produced, representing a large store of potential energy, which is made use of later on by the animal cell. It is true, however, that this assimilation and synthesis is associated with dissimilation, in the course of which the plant gives rise to waste products and generates certain forms of energy, such as motion, heat, light, and osmotic power. It is quite apparent, however, that in the case of the plants the kinetic energy is rather subordinate to the potential—a relationship which is reversed in the animal.

The energetics of a cell present themselves in various forms which, as we have just seen, may be grouped as resting or potential energy and as moving or kinetic energy. Among the former we have chemical, osmotic, cohesion and gravitation forces, and among the latter mechanical power, heat, light and electricity. But naturally, this classification is not fixed, because some of these energies may present themselves in either form. The chemical energy, for example, remains potential only as long as the atoms retain their position toward one another and becomes kinetic as soon as they rearrange themselves in accordance with their specific affinities. Thus, the animal receives potential chemical energy in the shape of complex organic substances and as oxygen. The regrouping of the former under the influence of oxygen eventually gives rise to carbon dioxid, water and simpler nitrogenous bodies as well as to a large amount of actual energy. Metabolism, therefore, is intended to keep the organism in energy-equilibrium. The chemical intake and outgo are balanced in such a way that the cells can continue to furnish the energy required of them. The metabolic equilibrium and the dynamical equilibrium must in the long run pursue a parallel course.

Living substance presents itself in many characteristic forms, the study of which has always been apportioned to morphology. It is true, however, that a hard and fast line between the structural and functional aspect of living matter cannot be drawn, because the former changes constantly under the influence of different physiological conditions. An organism is always in activity and conditions within it are never at a standstill, although in many cases these processes may be either very slow or too minute to be immediately apparent. Thus, the metabolic changes are balanced in such a way that the losses suffered in consequence of dissimilation are always made up, allowing the cell to increase its substance and to grow. Growth is the simplest manifestation of organic progress. In the second place, living substance in any form is capable of reproducing its like so that its continuance is assured as long as conditions favorable for its existence prevail. If the environment changes, living substance possesses

the power of adapting itself to the new conditions, provided, of course, that the change to which it is subjected, is not extreme. Hence, our conception of life is limited to such phenomena as metabolism, growth and evolution, reproduction, irritability and contractility, inclusive of motion.

General Conditions of Life.—The reason for the great diversity in the form of living matter must be sought in the conditions under which it is made to exist. Any change in the latter varies its metabolism, shape and energetics, but naturally, it would lead us altogether too far to study the different aspects of life in detail. In general, however, it may be stated that living matter presents certain internal as well as external characteristics. Among the former might be mentioned its structure, composition and physical properties, the study of which would necessitate an analysis of the cell and its component elements. Among the latter are to be noted the different conditions under which the cell is made to live, inclusive of the character of the medium, the temperature, the atmospheric pressure, osmotic pressure, moisture, and store of nutritive material.

As long as these conditions remain the same, life is said to be spontaneous. This term, however, is not a very good one, because life is never actually unconditioned. Thus, an organism leading apparently a perfectly spontaneous existence, is constantly under the influence of internal and external conditions. Its *spontaneity*, therefore, is only apparent, owing to the fact that the influences acting upon it are normal in their character and remain constant in their intensity. On the other hand, if the latter suddenly assume a different quality or become augmented by new conditions, the spontaneity immediately gives way to phenomena of *stimulation*. Hence a stimulation must result whenever the conditions of life are suddenly and markedly altered. In view of the fact that the latter are very numerous and relatively inconstant, the possibility of stimulation is always present, provided the protoplasm retains its receptive power.

Upon this basis, a *stimulus* may be defined as any extraordinary change in the conditions to which an organism may be subjected. While the number of stimuli is practically unlimited, it is possible to arrange them qualitatively in the following manner:

(a) Mechanical stimuli, inclusive of such influences as touch, pressure, stroking, pulling, the effects of gravitation, cohesion and adhesion, etc.

(b) Chemical stimuli, produced by various normal and abnormal substances. Among the former may be included the nutritive substances ordinarily required by living matter, and among the latter, practically any chemical agent with which it is accidentally brought into contact.

(c) Osmotic stimuli, consisting in changes in the osmotic pressure of the surrounding medium. As these alterations are commonly associated with chemical reactions, they are frequently included among the former.

(d) Thermal stimuli, produced by variations in the temperature of the medium.

(e) Photic or radiating stimuli, caused by changes in the intensity and quality of the light. Under this heading may also be placed the peculiar rays discovered

in more recent years by Hertz and Röntgen, and those emitted by uranium and radium.

(f) Electrical stimuli, produced by the exposure of the organism to the electrical current. Magnetic stimuli are no longer recognized, because it seems that living substance cannot be influenced by magnets.

Besides the quality of the stimulus, we must also take into account its "strength," this term being employed at this time in a quantitative way to characterize the sum total of its intensity, duration and frequency. Every organism is constantly under the influence of stimuli of all sorts which, as long as they retain a normal intensity, give rise to normal reactions. The conditions prevailing at this time, may be said to be *optimum* in their character. Living substance reacts toward these in the best possible manner. But, stimuli may also become excessive, and force the living substance to react maximally. It is only natural to assume that a continued *maximal* activity must finally produce injurious effects. Lastly, stimuli may possess so slight an intensity that they fail absolutely in producing an effect. *Minimal* stimuli, and especially *subminimal* stimuli, must eventually prove as dangerous to life as maximal ones.

FIG. 5.—INTENSITY OF STIMULATION.

L, life; *D*, death; *SMi*, subminimal; *mi*, minimal; *O*, optimum; *m*, maximal; *SM*, supramaximal stimuli; *T*, threshold.

It appears, therefore, that life is possible only between these two extremes and that death must result whenever this realm is exceeded in either direction. To begin with, therefore, living matter may be subjected to the subminimal stimuli toward which it does not react at all, at least not visibly. Eventually, however, a strength of stimulus will be reached toward which it reacts just barely. At the point where these *minimal* reactions just begin to appear lies the *threshold of stimulation*. If the strength of the stimulus is now increased still further, a point will be reached at which the reactions become *maximal* and finally, a point at which they show a *supra-maximal* character.

It should be emphasized, however, that the preceding outline cannot be applied rigidly in all cases, because living substance exhibits certain differences in its behavior which are dependent upon differences in its chemical and physical constitution. Thus, optimum conditions are not always found midway between the minimal and maximal extremes, and neither does a certain kind of maximal stimulus invariably cause fatigue or death. It is a matter of common observation that the energy contained in a stimulus is always very much smaller than the subsequent production of kinetic energy. To some extent living substance also possesses the power of adapting itself

to stimuli. Thus, while a certain stimulus may at first produce a maximal reaction, it often loses its stimulating qualities altogether in the course of time. This state of *adaptation* should be sharply differentiated from a somewhat similar one which is known as the *refractory* state. It has been previously emphasized that every activity of protoplasm incurs a certain destruction of material which must first be overcome by assimilation before another reaction can take place. Thus, if the dissimilation has been severe, or if the assimilation has been hindered in some way, the living substance suddenly finds itself unable to receive stimuli, or to develop them into a reaction. This period during which living matter remains, so to speak, impermeable to stimuli, is known as the *refractory period*.

The property of protoplasm to receive stimuli and to undergo in consequence of them characteristic chemical and physical changes, is known as *irritability*. Most generally, however, these alterations are not confined to the seat of the excitation but are propagated to other parts of its mass. This transmission of the waves of irritability is dependent upon its property of *conductivity*. In the multicellular forms, conduction between widely separated parts is greatly facilitated by the interposition of nervous tissue which is peculiarly suited for this function. The impulses leave these conducting paths eventually to be transferred to the constituents of the motor organ. The reception of an impulse by the cell is usually followed by the shifting of its constituents which in turn leads to a change in its form and position. This behavior of living matter is dependent upon its property of *contractility*.

SECTION II

PHYSIOLOGY OF MUSCLE AND NERVE

CHAPTER III

MOTION

Different Types of Motion.—The phenomenon of contractility consists in a shifting about of the constituents of the cell. It may be perfectly local or more far reaching, leading finally to changes in the shape and position of the organism as a whole. In this way, this liberation of energy gives rise to motion and locomotion, phenomena which the layman regards as the most certain proofs of life. The character of these movements is very manifold and is in keeping with the general structure and arrangement of the motor organs producing them. In general, it may be said that motion may be accomplished either passively or actively, in consequence of the following processes:¹

Motion	{	A. Passive		
		B. Active		
		{	Swelling of the cell wall	
			Changes in the cell-turgor	
			Changes in the specific gravity	
			Secretion	
			Growth	
			Contraction and expansion	{
			ameboid	
			ciliary	
			muscular	

A **passive motion** results whenever the power to move is not inherent in the object. Thus, if we observe the circulation of the blood under the microscope, the erythrocytes are seen to traverse the vascular channels with a certain speed, but this movement is imparted to them by an outside force resident in the musculature of the heart. We may also study the streaming of the protoplasm in such organisms as the rhizopods. We note here the slow progression of the granules to and from the cells, but they themselves are quite inactive and move solely in consequence of the flow of the medium in which they are contained. In this connection, mention should also be made of the so-called Brownian molecular motion which is displayed by many plant cells, and lower organisms. A very favorable object for observation is the unicellular green alga, called *closterium* (Fig. 6, I) which contains in each end of its crescent-shaped body a vacuole filled with fluid and fine granules (*K*). If the latter are observed under the high power of a microscope, they are seen to be engaged in an incessant trembling motion. The same pheno-

¹ Verworn's Allg. Physiol., Jena, 1909, and Winterstein's Handb. der allg. Physiol., Jena, 1912.

menon may be studied in the so-called salivary corpuscles (Fig. 6, II) which are dead leukocytes that have entered the saliva and have absorbed much water. The delicate molecular movement is displayed in this case by the fine granules situated in the immediate vicinity of the nucleus. Brown, who discovered this phenomenon in the cells of plants (1827), attributed it to the vibration of the molecules themselves and regarded it therefore as active. Wiener and Exner, however, have proved that it is passive, and that it represents an instability similar to that exhibited by the molecules of any liquid. The latter are never at a standstill, but always change their position and constantly move toward and away from one another.

Movements by swelling of the cell-walls are produced whenever the constituents of a dry, expansible body are brought into a moist medium so that they can attract molecules of water. The latter are stored in between them and force them apart until the body as a whole increases markedly in volume. As an example of this type of motion might be mentioned the so-called resurrection-plants found in desert regions. These plants may remain in a perfectly dried up condition for several years, their leaves being folded together like the fingers of a closed hand. When brought into a moist environment, they immediately unfold and assume definite shape.

Movements by changes in the cell-turgor are observed chiefly in plants. Inside the walls of the different cells is found a delicate protoplasmic sac, formed by the so-called primordial utricle. The latter is filled with a liquid, the cell-sap, the

FIG. 6.—BROWNIAN MOTION.

I. Closterium; with vacuole. II. Salivary corpuscle. (Verworn.)

FIG. 7.—SENSITIVE PLANT (*Mimosa pudica*). (Verworn after Detmer.)

A. Resting position. B. Stimulated.

concentration of which is varied by the addition of certain chemical substances which are formed in the course of the vital activities of these cells. As a result of the osmotic influx of water, the pressure in the primordial sac is increased. If the concentration of the medium is increased, water is abstracted from the cell. Variations in the pressure of the cell-sap may also be brought about by the contraction of the primordial utricle. Of greatest importance at this time, is the

fact that the tension or turgor existing in the sap-sac is brought to bear upon the elastic wall of the cell with the result that the size of the latter is either increased or diminished. In many plants these changes in the turgescence occur very suddenly and either spontaneously or in consequence of a stimulus of some kind. As an example of this type of motion might be mentioned the folding up and drooping of the leaflets of the sensitive plants (*mimosa pudica*), when touched or when exposed to low intensities of light. Sunlight, on the other hand, causes them to unfold and to erect their stems and leaflets. A similar phenomenon is exhibited by the insect-catching flowers of the carnivorous plants.

Movements by **changes in the specific gravity** may be observed in certain radiolaria. Ordinarily these organisms are heavier than water and creep along the bottom of stagnant pools. They are capable, however, of rising to the surface by generating small bubbles of carbon dioxide which are deposited among their protoplasmic streamers. At the surface this gas is quickly discharged. In consequence of the increase in their specific gravity then resulting they again sink to the bottom.

Movements by **secretion** result in algæ and oscillaræ and are produced by the projection from their bodies of a sticky liquid which adheres to the surface of the receptacle. As a result of this secretion the body of the organism is slowly forced forward in a definite direction.

Movements by **growth** are very general and occur whenever a cell increases its mass. But as the ordinary processes of assimilation are slow, the detection of this movement often necessitates a comparison of conditions at different periods of the life of the organism. Many seedlings display a more perceptible growth. Moreover, many seeds and fruits require only the slightest touch to make them burst and to discharge their contents. In these cases the mechanical energy developed by growth has been stored, and has placed the capsular investment under a high degree of tension.

The alternate **contraction and expansion** of a mass of protoplasm means that it assumes a rounded shape during the former phase and a flat outline during the latter. Its surface, therefore, undergoes constant changes, but naturally, only those organisms can display this phenomenon

in a plastic manner which possess a liquid consistency. We have previously seen that this characteristic is universal among living substance, but whether an organism as a whole is motile, depends, of course, upon the character of its framework which may or may not be sufficiently yielding to permit the contraction of its protoplasm. Three types of structures are evidently well adapted for this purpose, namely, (a) small masses of living substance which are not surrounded by a distinct cell wall, (b) hair-like protoplasmic processes with which many cells are beset, and (c) the muscle cell as it appears in striated, non-striated and cardiac tissue.

Ameboid Movement.—When placed upon a slide under the microscope, an ameba-cell appears as a gray droplet embracing a nucleus and contracting vacuole. Its central portion, consisting of endoplasm, contains as a rule a number of granules, while its peripheral zone, or exoplasm, is more or less hyaline. When kept under optimum condi-

FIG. 8.—DIATOMAE, SHOWING PROTRUSION OF MUSCULAR MATERIAL. (Verworn.)

tions, this droplet of living substance sends out lobate processes into the surrounding medium which are constantly increased in size and length. These feelers, or pseudopodia, may be sent out in all directions, or may be restricted to one particular locality. In the latter case, the entire mass of the cell may eventually be transferred into one of these projections, occasioning in this way a slow onward streaming of the protoplasm and its admixtures. This centrifugal movement, however, may be changed at any moment into a centripetal one by stimulation. The cell then assumes a nearly spherical outline, representing the state of contraction.

This type of movement is not confined to the ameba, but is also exhibited by the rhizopods, the egg cells of certain animals, pigment and giant cells and the leukocytes of the blood. In the leukocytes it

FIG. 9.—AN AMEBA, SHOWING DIFFERENT STAGES OF MOVEMENT. (Verworn.)

serves the primary purpose of engulfing nutritive particles, so that these may be digested and assimilated by the living substance. It is also made use of in ridding the body of toxic materials of all sorts, this process having been designated by Metchnikoff as phagocytosis. In the plant cells in which this protoplasmic streaming is very general, it serves the additional purpose of disseminating the food substances.

Ciliary Movement.¹—Cilia are cellular appendages possessing the shape of slender, tapering hairs. Their length varies greatly in different animals. In the trachea of man, for example, they measure 0.003–0.005 mm. in length and 0.0003 mm. in thickness. Their number also varies. Some of the infusoria, such as paramecium, are beset with several thousands of them, while an ordinary lining cell of the digestive or respiratory passage may possess only several hundreds of

¹ Engelmann, in Hermann's Handb. der Physiol., 1879, i, 380; Pütter, Ergebn. der Physiol., i, 1903, and Verworn, Allg. Physiol., Jena, 1910.

them. While their number is generally proportional to the size of the cell, it may also happen that a single cell is equipped with only one or several cilia. When especially long and thick, they are known as flagellæ. In the protozoa, these ciliated cells usually extend over the entire surface, while in the metazoa they occupy more restricted regions of the body. They are found, for example, (a) upon the ova and embryos of many invertebrates, fish, and amphibia, (b) upon the epidermis and in the digestive tract of the coelenterates, worms, echinoderms, and molluscs, (c) in the respiratory passage of molluscs, amphibia, fish, birds and mammals, and (d) in the urogenital tract of vertebrates. In man, they are in evidence upon the mucous membrane of the nose, lacrimal duct and sac, Eustachian tube and tympanic cavity, upper portion of the pharynx, larynx with the exception

FIG. 10.—CILIATED CELLS.
A, from a liver duct of the garden snail; B, from mucosa of frog. (After M. Haidenhain.)

FIG. 11.—MOVEMENT OF A SINGLE ILIUM.
A, Progressive in direction of arrow; B, Regressive. (After Verworn.)

of the vocal cords, trachea and bronchi, uterus, Fallopian tube, vagina, central canal of the spinal cord and the cerebral ventricles. During embryonal life ciliated epithelium is also present in the mouth, esophagus and stomach

The phenomenon of ciliary motion is brought about by a peculiar to and fro movement of these projections.¹ Being firmly anchored in the outer portions of the cells, they swing like pendula along parallel planes and thus avoid striking one another. In many cases, however, the planes in which they move are not straight, but curved, simulating circles, ovals, or even the course of a whip-lash. The latter is especially true of the flagellæ with which, for example, sperm cells are beset. Moreover, if our attention is directed to a single row of cilia, it is noted that this movement is progressive in character, beginning with their position of rest. The latter may be determined most easily by rendering them inactive by means of a narcotizing agent. At this

¹ Erhart, Studien über Flimmerzellen, Archiv für Zellforschung, xxxi, 1910.

time, the different cilia do not project vertically outward, but are more or less bent. When contracting the cilium curves strongly toward its vertical position, its convex border being at first strongly inclined in this direction. Having reached its extreme position on the other side of the vertical line, it returns to the position of rest by the process of relaxation. The former movement is, of course, more rapid than the latter and constitutes the effective stroke of the cilium. It is accomplished by the contraction of the ciliary substance situated on the side toward which the stroke is being directed, the opposite side meanwhile being put on the stretch. The contraction having been completed, the cilium is forced into its original position in consequence of the elastic recoil of the stretched side.

If a cell is beset with only one of these hair-like projections, an interference with its motions is not likely to occur, but as there usually are a number of cilia situated upon a single cell, the question may be asked how they can avoid beating against one another. Their strokes are of course very rapid, so that the eye is scarcely able to follow them. We thus obtain merely the impression of a general motion which, however, it is possible to render more conspicuous by adding some granular material to the medium in which they are contained. The individual granules will then be forcibly thrown in the direction of the effective stroke of the cilia. The character of their beat may be studied more advantageously in preparations which have been under observation for some time, because the movements of dying cilia gradually become less rapid until eventually a number of them may be found which beat only at intervals. Their movements may also be considerably retarded by moistening them with a few drops of ice-cold saline solution. Under ordinary conditions the cilia of the frog's pharynx beat at the rate of 12 times in a second. Their contractions, however, do not take place simultaneously but successively, those in the front row of each field becoming active first, those in the second next, and so on, until the last one has been involved. In this way, it is brought about that the cilia of each field present all the different stages of contraction and relaxation and give the impression of regular waves passing over them.

The regular sequence of these waves of contraction is not effected with the aid of nervous structures, but is dependent upon a protoplasmic continuity between the different cells. Naturally, this action arises in consequence of extraneous stimuli, but the impulses themselves are generated in the cilium, or rather, in the cell to which it is attached. That this is so, may be gathered from the fact that the cilium ceases to beat, if broken off at its base, but continues to act if left in contact with at least a small fragment of the cell in the vicinity of its root. The contraction of the cilia takes place with rhythmic regularity; moreover, since it occurs without the intervention of the nervous system, it may be said to be automatic in its character.

The function of the cilia is entirely mechanical, in that they impart

motion to the organism as a whole or cause bodies to move with which they are brought into contact. Thus, the cilia lining the upper digestive tract of the frog, beat in the direction of the stomach so that those small particles which are beyond the reach of the process of deglutition, are nevertheless projected into this organ. In the respiratory passage, their effective stroke is directed toward the mouth with the result that the air-passages are constantly cleared of dust and mucous globules. In the female genital tract they beat in the direction of the external orifice, and thus exert a stimulating action upon the spermatozoa, forcing them to progress directly against the ciliary stream. In those protozoa in which the entire external surface, or parts thereof, are beset with cilia, they impart a motion to the entire organism in a direction opposite to that of their effective stroke. They act in this case in the manner of the lateral fins of the fish. As far as the work performed by the cilia is concerned, little can be said. Jensen¹ states that the cilia of a paramecium possessing a length of about 0.25 mm., are able to raise a weight of 0.00158 mgr., or about nine times the actual weight of one of these cells.

Muscular Movement.—In the higher forms, all motions, as well as the movements occurring inside the body, are carried on with the help of specialized cells forming the so-called muscle tissue. These elements appear first of all in the infusoria, such as stentor and vorticella. If one or the other of these organisms is observed under the microscope, its protoplasm will be seen to be permeated by a number of long extended fibrillæ, the so-called *myoids*. In stentor, these fibrillæ are arranged singly below the surface of the trumpet-shaped body, while in vorticella they are cemented together to form a thick stalk upon which the bell-shaped upper portion of this organism is situated. When in a condition of rest, their long bodies extend far out into the medium. Upon stimulation their head portions are swiftly retracted toward the surface to which they are attached. This change in their shape and position is made possible by the contraction of these elementary muscle cells.

Broadly speaking, these contractile fibrillæ reappear in the higher animals in the shape of the smooth or *non-striated* muscle cells. Besides, a second type of cell is found here which possesses a much greater complexity of structure and forms the chief constituent of *striated* muscle. The first enter very largely into the formation of what might be termed the *visceral musculature* which performs work in the interior of the body, while the latter constitute the *skeletal musculature* which is concerned with the regulation of the position of the animal in space. The striated is under the direct control of the will, while the non-striated is not, and has to do solely with the vegetative processes of life. Besides these, the animal body also contains a third type of contractile tissue, namely the *cardiac muscle*, but the function of this one is

¹ Pfüger's Archiv, liv, 1893, 537.

more specific, because it develops the pressure which is required to drive the blood through the circulatory channels.

The principle of action, however, is the same in all three cases, because every muscular movement consists of two phases, namely, a period of contraction and a period of relaxation. During the former stage the individual cells or fibers shorten and thicken, while during the latter they assume their original long and thin shape. Obviously, if each constituent undergoes these changes, the muscle as a whole must present very similar alterations. Its contraction is characterized by a decrease in its length in favor of its breadth, and its relaxation, by a decrease in its breadth in favor of its length. During the first period, therefore, its outline is more spherical.

FIG. 12.—STENTOR CERULEUS, SHOWING MYOIDS.

A, position of rest; B, contracted state upon stimulation.

FIG. 13.—VORTICELLA.

A, resting position; B, contracted upon stimulation.

The Structure of Muscle Tissue.¹—The chief element of muscle tissue is the muscle cell which, in the case of the *striated* type, is generally designated as a fiber. The latter term seems the more appropriate, because they may attain a length of 30 to 40 mm. or, as some authors claim, of 100 to 150 mm. Their thickness varies between 0.1 to 0.01 mm., differing not only in different muscles, but also in the same muscle. Their thickness, in particular, may be much increased by exercise and also during certain pathological conditions, such as hypertrophy and dystrophia muscularis. If we confine ourselves to the striated type, constituting the mass of the skeletal musculature, we find that each muscle is invested by a connective-tissue sheath (perimysium) which then extends into its interior (epimysium) and forms small compartments in which the individual muscle fibers are con-

¹ Kollicker's *Gewebelehre*, Leipzig, 1889, and Schafer, *Essentials of Histology*, London, 1916.

tained. This connective-tissue reticulum serves as the highway for the local blood-vessels and nerves. If one of these fibers is examined in cross-section, it appears as a rounded area possessing a rather dark granular center and a lighter non-differentiated outer zone, or sarcolemma. In longitudinal section, these fibers are cylindrical in shape and rounded at their ends, where they are joined with neighboring ones by means of connective tissue. They do not branch as a rule, but those of the tongue and skin divide into finer filaments which are finally inserted in the mucous membrane.

FIG. 14.—MUSCULAR FIBERS OF THE ADDUCTOR MAGNUS OF A DOG.

M, muscular fiber; *n*, nuclei; *s*, sarcolemma; *ee*, spaces left by the retraction of the muscular substance from the interior of the sarcolemma. (*Ranvier*.)

Each fiber consists of a thin, hyaline sheath, or sarcolemma which fulfills the purpose of a cell membrane, and should not be confounded with the more external connective-tissue envelope. These saccules are filled with soft contractile protoplasm arranged in alternate discs of dark and light substance. The former which is doubly refracting, or anisotropic, forms the so-called *transverse discs*, and the latter which is singly refracting, or isotropic, the so-called *lateral discs*. In the middle of the clear band is seen a very delicate dark line which has been regarded by Krause as a dividing membrane to mark off definite segments, called sarcomeres. In accordance with the preceding terminology, these lines may be referred to as the *intermediate discs*. Each fiber is provided with a number of nuclei which, in mammals and birds, are situated directly below the sarcolemma and are embedded in a mass of sarcoplasm. Owing largely to the transverse bands which recur in numbers of close to 10,000 for each 1 cm. of distance, these muscle fibers present a distinct striated appearance.¹

These fibers also display a delicate longitudinal striation, for the reason that each fiber is really made up of a number of extremely fine contractile filaments which are arranged parallel to one another. They are known as the primitive *fibrillæ* or *sarcostyles*. These fibrillæ are closely packed together in sarcoplasm which unites them in turn with the fibrillæ of neighboring fibers. Hence, each striated muscle fiber consists of fibrillæ, sarcoplasm and sarcolemma. A large number of fibers (2000) are bound together into muscle-bundles which are separated from one another by the epimysium, and many bundles into a muscle which is enveloped externally by the perimysium. This arrangement may be brought out most clearly in a muscle which is copiously supplied with sarcoplasm, by hardening it in alcohol. Naturally, each fibrilla presents alternate discs of dark and light substance, the different fibrillæ of the fibers being arranged in such a way that their cross-bands come to lie in practically the same horizontal plane. In this connection it should be remembered that some of the higher vertebrates are in possession of two types of striated muscle tissue which is either rich or poor in sarcoplasm. In fact, certain animals, such as the rabbit and different fish, possess certain muscles which are composed of only one type of fibers and thus present either a dark or a light appearance. The former are commonly designated as red (semitendi-

¹ Gutherz, Archiv für mikr. Anat., lxxv, 1910.

nosus) and the latter as pale muscles (adductor magnus). It is readily conceivable that this peculiarity in the chemical nature of the different muscles must

FIG. 15.—MUSCLE FIBER OF MAMMAL HIGHLY MAGNIFIED, SHOWING ITS TRANSVERSE AND LATERAL DISCS. (*a*, from Schäfer; *b*, from Sharpey.)

lead to differences in the strength and speed of their contraction. Thus, it is found that the dark muscles are best adapted for the lifting of heavy loads, while the pale muscles excel rather by their greater rapidity of contraction. The latter, however, are more easily fatigued.

The more primitive *smooth muscle tissue*¹ consists of spindle-shaped cells possessing either a cylindrical or a slightly flattened outline. Their length varies between 45 and 225 μ and their thickness between 4 and 7 μ . During pregnancy, the cells of the uterus frequently attain a length of 0.5 mm. Inasmuch as these cells are also composed of a number of fibrillæ, they exhibit a delicate longitudinal striation. Their nucleus occupies a central position and possesses a long-oval shape which, however, becomes more rounded during the contracted condition of the cell. In its immediate vicinity, as well as in the tapering ends of the cell, is found a considerable amount of undifferentiated protoplasm or sarcoplasm. While the striated muscle cells are generally bound together to form compact, rounded masses, the smooth muscle cells are usually embedded in a heavy substratum of connective tissue, and the tendency is to spread them out in the form of membranes.

FIG. 16.—SENSORY NERVE TERMINATIONS IN ARBORIZATIONS AROUND THE ENDS OF MUSCLE-FIBERS. (*Ceccherelli*.)

¹ McGill, *Am. Jour. of Anatomy*, ix, 1909.

Cardiac muscle tissue occupies a special position, because embryologically as well as histologically it appears in the form of modified contractile fibers. This is especially evident in the lower vertebrates in which these cells possess a spindle-shape, a marked cross-striation, and a long-oval nucleus. In mammals, the cardiac muscle cell appears as a short cylinder which is usually united with a neighboring one by an oblique process to form a muscular plexus.¹ Functionally it is of interest to remember that these prolongations bring the cells of adjoining rows or

FIG. 17.

FIG. 17.—FIBRILS OF THE WING MUSCLES OF A WASP, PREPARED BY ROLLETT'S METHOD. HIGHLY MAGNIFIED.

A, a contracted fibril; B, a stretched fibril with its sarcous elements separated at the line of Hensen; C, an uncontracted fibril showing the porous structure of the sarcous elements. (Schäfer.)

FIG. 18.

FIG. 18.—SMOOTH MUSCLE CELLS, TEASED APART AND SHOWING LONG OVAL NUCLEI SURROUNDED BY UNDIFFERENTIATED PROTOPLASM.

areas into closer relation. The oval nucleus occupies a position in the axial portion of the cell which also contains much undifferentiated protoplasm, or sarcoplasm. The other parts of the cell exhibit a very delicate cross-striation.

The Action of Striated Muscle in Locomotion.—As far as the mechanical properties of the resting muscle are concerned, we have previously seen that it is a very yielding tissue and possesses a soft consistency so that its shape may be varied with ease. The contracted muscle, on the other hand, is firm to the touch and exhibits a more rounded outline, because its length is diminished in favor of its breadth.

¹ Zimmermann, Über den Bau der Herzmuskulatur, Archiv für mikr. Anat., lxxv, 1910.

Thus, as most striated muscles are affixed to the skeleton in such a way that one of their ends is stationary and the other freely movable, their contraction invariably results in a closer approximation of their points of insertion and attachment. In this way, movements are produced which, if the bones are employed as levers, give rise to locomotion.

A lever is a rigid bar, one part of which is relatively fixed and the other freely movable. It possesses a point of support, or *fulcrum*, a point of resistance, or *weight*, and a point to which the force, or *power* is applied. In accordance with the relative positions of these points, we recognize three different systems of levers, namely:

(1) The fulcrum is placed between the power and the weight. When this lever is moved, the weight and the power describe arcs the concavities of which are turned toward one another.

FIG. 19A.—CARDIAC MUSCLE.

FIG. 19B.—SINGLE CARDIAC CELLS. Magn. 1000.

(2) The fulcrum is at one end and the weight between it and the power. The arcs described by the weight and the power are concentric, but the weight moves less.

(3) The fulcrum is at one end and the power between it and the weight. The arcs are concentric, but the weight moves a greater distance than the power.

As an example of a lever of the first order might be mentioned the movement of the skull upon the spinal column. The articulation between the axis and occipital bone serves in this case as the fulcrum, the face as the weight and the posterior muscles as the power. As an example of a lever of the second order may serve the foot when employed to raise the body upon the toes. The fulcrum is formed in this case by the toes resting upon the ground, the weight by the body resting upon the ankle-joint and the power by the gastrocnemius and soleus muscles. As an example of a lever of the third order might be mentioned the arm when it executes the movement of flexion. In this case, the fulcrum is formed by the elbow-joint, the weight by the hand and the power by the biceps muscle, the tendon of which is inserted in front of the elbow-joint. These three systems may also be illustrated by giving to the foot the three different positions indicated in Fig. 21.

Theories of Muscular Contraction.—The contracting striated muscle also presents certain microscopic changes which have been employed in the formulation of several theories regarding the manner in which the contraction is brought about. To begin with, it should

FIG. 20.—DIFFERENT SYSTEMS OF LEVERS.
F, fulcrum; *P*, power; *W*, weight.

be remembered that the different elements composing a muscle, do not contract simultaneously, but successively, those nearest the seat of the stimulation being activated first. Consequently, the contraction progresses over the muscle in the form of a wave which is directed toward the part farthest removed from the point stimulated. The

FIG. 21.—DIFFERENT POSITIONS GIVEN TO THE FOOT IN ILLUSTRATION OF THE THREE SYSTEMS OF LEVERS.

details of this wave of contraction may be studied under the microscope in fresh preparations of muscle from the legs or wings of insects. Moreover, if a muscle is dropped into alcohol or osmic acid, a series of waves are evoked in its component fibers which are then fixed as nodular or fusiform swellings.

It is commonly believed that the primary source of the energy of muscle is to be found in the interaction of several of its chemical constituents. The potential energy here stored is transformed into kinetic energy of the mechanical variety in accordance with the law of the conservation of energy. Thus, the resting muscle represents an unstable system which may readily be transformed by the mere application of a stimulus. The question now arises, how is it possible that this explosive process leads to a shortening of the individual muscle fibers as well as of the muscle as a whole? Several explanations are at hand, although the best of them cannot be said to be absolutely satisfactory.

Weber¹ has claimed that the contraction of muscle results in consequence of the sudden alteration of its elastic power, this change being brought about by a chemical transformation following in the wake of the stimulus. These internal chemical forces tend to cause variations in the elastic equilibrium of the muscle, leading to a change in its form. In accordance with the view of Mayer (1845), muscle tissue may be compared to a steam engine which transforms the heat generated by it into mechanical energy. Engelmann² assumed later on that the heat evolved results in a transfer of molecules of water and a change in the form of the muscle as a whole.

This assumption has given rise to the so-called thermodynamic theory of muscular contraction which is based upon the observation that the contracting fiber suffers an inversion of its elements, *i.e.*, the dark discs become more fluid and lighter in color, while the light discs become more compact and darker. But as the width of the contracting portion of the fiber becomes greater, both bands must be pushed out laterally and must therefore decrease in height. Engelmann then assumed that the contraction of the fiber is caused by a rapid transfer of water from the isotropic into the anisotropic substance under the influence of the chemical energy set free in the form of heat. This imbibition with molecules of water tends to impart a more oval or spherical shape to the individual contractile elements. Later on, as the heat is dissipated, the water again returns into the light substance and causes the fiber to relax. Engelmann has imitated this process of swelling

FIG. 22.—ARTIFICIAL MUSCLE.

The artificial muscle is represented by the catgut string, *m*. This is surrounded by a coil of platinum wire, *w*, through which an electrical current may be sent. The catgut is attached to a lever, *h*, its fulcrum is at *c*. The catgut is immersed in a beaker of water at 50° to 55° C., and "stimulated" by the sudden increase in temperature caused by the passage of a current through the coil. (Howell, after Engelmann.)

¹ Muskelphysik., 1846.

² Pflüger's Archiv, xi, 1875, 432 and xxv, 1881, 538.

and shortening with the help of a violin string which he first passed through a coil of platinum wire and then attached under some tension to a writing lever. If this string was immersed in water and then subjected to heat by passing an electrical current through the wire, it shortened very considerably. The subsequent discontinuance of the current permitted the string to regain its original length. The curves recorded in this manner are very similar to those obtained with muscle preparations under ordinary conditions of experimentation.

Ranvier¹ agrees with Engelmann in so far as he believes that the anisotropic substance is the only contractile part of the fiber. He holds, however, that the anisotropic discs lose water on contraction which is transferred to the interfibrillar substance. Schäfer² adheres to Engelmann's hypothesis and states further that the anisotropic substance is permeated by minute channels which run parallel to the axis of the fiber and serve to accommodate isotropic material. In consequence of the filling of these canaliculi the individual segments or prisms of the anisotropic substance are forced farther apart, causing a widening of the fiber on contraction.

Absorption is also the principle of the hypothesis of McDougall.³ It is believed that the sarcostyles or fibrillæ of striated muscle are constructed in such a way that their distention immediately produces a reduction in their length. This distention is assumed to take place as a result of an influx of the sarcoplasmic fluid which surrounds them. Meigs⁴ has applied this conception to smooth muscle and claims that its contraction is dependent upon the passage of fluid from the cell into the interstitial spaces.

A hypothesis has also been formed by Müller⁵ which attributes muscular contraction to an electrical attraction and repulsion of doubly refracting crystalloids. In consequence of a production of heat, these bodies change their potential, relaxation resulting when the polarity subsides owing to the equalization of the temperature. It is a well-known fact that muscular contraction, as well as any other activity of protoplasm, is associated with electrical variations, but these changes have been proved to be quite independent of contractility.⁶ All these hypotheses are very indefinite. Based upon the work of Berthold⁷ a hypothesis has been formulated by Verworn⁸ which holds that the chemical changes in muscle result in alterations in the surface tension of the isotropic and anisotropic discs. In consequence of these variations, the histological constituents of muscle change their power of cohesion and adhesion and hence, their shape and position. Jenson⁹ has put forward the so-called coagulation-hypothesis which bases the contraction of muscle upon changes in the aggregate condition of the sarcoplasm. In accordance with this view, its relaxation is not regarded as a passive phenomenon, but is said to occur in consequence of processes the reverse of the former.

It is to be noted especially that the contraction of muscle requires merely an internal readjustment of its constituents and does not involve changes in its volume which could only be had by a transfer of material from and to other tissues. This fact may be proved by placing a muscle in a glass receptacle filled with boiled saline solution, and equipped with a capillary tube in which the water

¹ *Lçons d'anat. gén. sur le syst. muscul., Paris, 1880.*

² *Proc. Royal Society, xlix, 1891.*

³ *Journ. of Anat. and Physiol., xxi, 1897; 410; and xxii, 1898, 187.*

⁴ *Am. Journ. of Physiol., xxii, 1908, 476; also Hürthle, Pflüger's Archiv, cxxvi, 1909, 1.*

⁵ *Theorie der Muskelkontraktion, Leipzig, 1891.*

⁶ *Helmholtz (1855) and Biedermann, Elektrophysiol., Jena, 1895.*

⁷ *Studien über die Protoplasma Mechanik, Leipzig, 1886.*

⁸ *Allg. Physiologie, Jena, 1910; and Saleotti, Zeitschr. für Allg. Physiol., vi, 1906.*

⁹ *Pflüger's Archiv, cxxxvii, 1901, 367.*

forms a meniscus. If the muscle is now made to contract, it will be seen that the meniscus does not move.

The Excitation of Muscle.—We have seen that all movements which are to be carried out with precision, are effected by means of striated muscle. In nearly all cases this tissue is under the control of the central nervous system and especially of the cerebrum which gives rise to volition. Non-striated muscle, on the other hand, is not absolutely dependent upon central nervous structures, but is regulated by peripheral or local centers. For this reason, it is able to show a marked degree of spontaneity and is, therefore, not wholly under the guidance of the will. It is true, however, that its independency is not absolute, because its connection with the cerebrospinal system is necessary to bring it into functional relation with other parts of the body.

The different muscles are connected with the central nervous system by means of nerves which conduct impulses either toward them or away from them. Hence, muscle tissue must be in possession of two types of end-organs, namely one for the reception of the stimuli and one for the production of the motor reaction. The sensory end-organ or *muscle-spindle*, is composed of a group of delicate fibers which are invested by a thick covering of perimysium. Around these the nerve terminals are arranged in the form of spirals or rings. The motor end-organ, or *motor plate*, consists of a bulbular enlargement of the axis cylinder which is pressed flat against the sarcolemma of the muscle fiber. It appears as a rounded granular mass, the substance of which contains numerous nuclei. It is invested solely by neurolemma which is directly continuous with the sarcolemma. The medullary sheath disappears at some distance from the motor plate,

namely, at the point where the nerve fiber begins to divide to form this ramification of axis cylinders. Most generally, a single muscle fiber contains only one of these motor plates, but if it is very long, it usually embraces two or several of these endings. The different nerve fibrils arising from these plates, unite into larger ones so that their number is much reduced when leaving the muscle. That this is a very economical arrangement may be gathered from the fact that inasmuch as a muscle, such as the oculomotorius, contains about 15,000 muscle fibers, about 180 million nerve fibers would be required for 30,000 grams of muscle substance. Stilling, however, has found only about 30,000 fibers in the anterior roots of the spinal cord. In smooth muscle, the individual nerve fibers terminate in complicated networks which are

FIG. 23.—SCHEMA TO SHOW THAT CONTRACTING MUSCLE DOES NOT CHANGE ITS VOLUME.

M, meniscus of saline solution; S, electrodes through which muscle in receptacle is stimulated.

beset with ganglion cells. From these plexuses delicate fibrils then pass to the different muscle cells.

Under ordinary conditions, a muscle contracts only in response to impulses generated in the central nervous system and conveyed to it through its nerve. Under experimental conditions, however, these impulses may be generated anywhere along the course of the nerve, and most easily by electrical or mechanical stimuli. The natural excitatory agents are usually designated as *adequate* stimuli and the uncommon ones, as *inadequate* stimuli. It is also possible to produce a contraction of a muscle by stimulating it directly. In the latter case the stimulation is said to be *direct*, while the activation of the muscle through its nerve constitutes the method of *indirect* stimulation.

FIG. 24.—INDEPENDENT IRRITABILITY OF MUSCLE.

A, dorsal lymph sac into which curare is injected; L, ligature upon left thigh. The stimulation of the sciatic nerve at 1 is then effective but ineffective at 2. Both gastrocnemius muscles, when stimulated directly at 3 and 4, give a contraction.

Independent Irritability of Muscle.—If a muscle is stimulated directly, it may be contended that it reacts in consequence of the excitation of its nervous constituents and not on account of the excitation of its myoplasmic elements. Obviously, it is quite impossible under ordinary conditions to differentiate between these two factors, unless one of them can be rendered temporarily useless. An experiment¹ enabling us to exclude the nervous elements may be performed as follows: Having isolated the sciatic nerve of a frog in the region of the thigh, a ligature is tightly drawn around all the other tissues of this part. The blood supply having thus been cut off from this extremity, a few drops of curare² are injected into the dorsal lymph-sac. About 20 to 30 minutes later, the opposite sciatic nerve is isolated, and a small opening made in the skin over each gastrocnemius muscle.

As soon as the curare has taken effect, the stimulation of the sciatic nerve fails to evoke a contraction of the gastrocnemius on the side which has not been ligated (at 2), but produces a reaction on the side of the ligature (at 1). If the gastrocnemii muscles are now stimulated directly (at 3 and 4), it will be found that both are responsive. By applying a galvanometer to the sciatic nerve of the leg which has not been ligated, it may readily be proved that this nerve has retained its functional power, because every stimulus gives rise to a deflection of

¹ Archiv für path. Anat., 1856, or Claude Bernard, Comp. rend., 1856, 825.

² Curare, wurare or urare is a poison used by South American Indians upon arrows and other weapons. It is prepared from the roots of the wurare plant, a concoction being formed with other ingredients to hide the real active principle.

the needle of this instrument. The above results clearly show that the curare has destroyed the connection between the nerve and the muscle substance. In other words, this agent has paralyzed the motor plate, so that the centrifugal impulses can no longer reach their destination. On the side on which the curare has been prevented from producing its characteristic effect by the ligature, the impulses pursue as before a perfectly straight course into the muscle. The latter fact may also be demonstrated by stimulating the central end of the sciatic nerve on the curarized side. The impulses here generated now travel in a centripetal direction into the cord, whence they attain the opposite gastrocnemius muscle by the sciatic nerve of the non-curarized side. Clearly, therefore, the normal muscle may also be stimulated reflexly.

The chief conclusion to be derived from this experiment, is this: Inasmuch as the nervous elements in the muscle have been rendered functionally useless by the curare without destroying the susceptibility of the muscle substance to direct stimulation, it must necessarily follow that the myoplasm is independently irritable. In other words, normal myoplasm is capable of receiving stimuli and of reacting even without the aid of nervous tissue. This conclusion may be substantiated by other facts. Thus it has been observed that the hearts of embryos possess rhythmical activity long before any nerve tissue can be recognized within them. Moreover, if the motor nerve of a muscle is cut, it undergoes degenerative changes and finally becomes functionally useless. At this time, however, it is still receptive to direct stimulation. Kühne, moreover, has observed that the sartorius muscle of the frog reacts even if stimulated at its very end, in spite of the fact that its ends are devoid of nerve fibers. In addition, Schiff has shown that dying muscle reacts toward mechanical impacts by a local contraction, *i.e.*, the fibers near the seat of the irritation are drawn together into a nodular swelling.

CHAPTER IV

THE GRAPHIC REGISTRATION OF MUSCULAR CONTRACTION METHODS OF STIMULATION OF MUSCLE AND NERVE

A. Muscle-nerve Preparation.—While no serious objection can be raised against the use of almost any muscle, our knowledge regarding the behavior of this tissue has been gathered chiefly from preparations of the gastrocnemius and sartorius muscles of the frog, owing to the relative ease with which they may be isolated and rendered accessible to the recording apparatus. It is also true that the muscles of cold-blooded animals retain their irritability after their removal from

the body for a much longer time than those of warm-blooded animals. It is a simple matter to reflect the skin from the leg of a pithed frog and to isolate the gastrocnemius muscle by cutting through the tendo Achillis and the fascia uniting it with the neighboring tibia. This bone is then cut through directly below the knee-joint. Above the latter is found the sciatic nerve which may be traced along the posterior aspect of the thigh into the pelvis where its three roots are seen to arise from the posterior end of the spinal cord. It should be divided at this point and carefully separated all the way down to the muscle with

FIG. 25.—MUSCLES OF HIND LEG OF FROG. (Ecker.)

which it must of course be left in contact. The fibers of the gastrocnemius muscle are short and are arranged obliquely into a compact mass of tissue. For this reason, the actual shortening of this muscle is really quite inconsiderable in comparison with its power of contraction. In the sartorius muscle, on the other hand, the fibers are long and are placed more parallel to one another. This is also true of the gracilis and semimembranosus muscles. Preparations of the latter give high contractions, but the weight which they are able to lift is relatively small.

Methods of Registration. *Myography.*—Soon after the experiments of E. Weber (1846), pertaining to the elasticity of muscle,

Helmholtz (1850–1852), devised a recording apparatus which he designated as a myograph. This instrument has subsequently been modified by Pflüger, Fick and Du Bois-Reymond. It would lead us altogether too far to give even a tolerably accurate description of these and other graphic appliances, and hence, it may suffice to say that the registration of the contraction of muscle necessitates first of all a means of holding the muscle, secondly, an outfit for recording its movements, and thirdly, a surface upon which this record may be made. One end of the freshly excised muscle is fastened in a stationary clamp, while the other is connected by means of a string with a writing lever placed horizontally underneath it. This lever should be

FIG. 26.—A METHOD USED TO REGISTER MUSCULAR CONTRACTION.

St, stand for holding of clamp *C* and writing lever. *WL*, the muscle *M* is attached to the lever by means of a small hook and string. The lever is counterpoised by weight *W*. The stimulation is effected through the electrodes, *S*. The speed of the kymograph *K* may be varied by fan *F*.

properly counterpoised by weights or tension springs so as not to extend while it rests. Moreover, the muscle should be surrounded by a small bell jar so as to be able to keep it under proper conditions of moisture and temperature. The recording surface generally employed to-day, consists of a sheet of glazed paper which is attached to the cylindrical drum of a kymograph and is then evenly covered with soot by rotating it in a broad gas flame. The drum carrying the blackened paper, is moved by clockwork at different speeds, the velocity of its movement being indicated in seconds by a chronograph which is adjusted underneath the muscle lever. If the rotation is rapid, an ordinary tuning fork may be permitted to register its vibrations below the myogram.

Isotonic and Isometric Myograms.—If a muscle is made to contract after it has been attached to the writing lever, it must suffer an initial stretching and this stretching must be the greater, the heavier the load against which it acts. A certain part of its energy, therefore, must be lost without being able to produce a visible effect. To counteract this distention, it is customary to after-load the muscle with a slight weight which is neither increased nor diminished during the contraction, or to hold the writing lever in a horizontal position by means of a support or a tension spring. While thus subjected to the least possible tension, it is not hindered in changing its length and in generating

FIG. 27.—DIFFERENT WAYS OF COUNTERPOISING THE WRITING LEVER. A, B and C, isotonic arrangements; D, isometric arrangement; S, spring.

visible mechanical energy. A myogram obtained under this condition is characterized as isotonic. As far as the adjustment of the muscle and weight is concerned, the latter may be affixed (a) directly beneath the point of attachment of the muscle (method of loading), (b) precisely in the same place with this modification, however, that the lever is held in a horizontal position by a counterpoising load or other appliance (method of after-loading), and (c) to the axis of the lever by means of a pulley. The latter arrangement gives the most perfect isotonicity.

If the muscle is attached near the fulcrum of the writing lever,

while at the same time the long arm of the latter is prevented from moving upwards by a counter force, such as a spring (Fig. 27D), the shortening of the muscle will be insignificant in comparison with the tension to which it is subjected. A curve of this kind, displaying almost no change in the length of the muscle and practically no mechanical energy, is characterized as isometric. In this way, a relatively much larger proportion of the total energy liberated is transferred into heat. While the muscles ordinarily used by us in the production of work, are not arranged in a strictly isometric manner, our contractions most generally possess an isometric character for the reason that they are executed against resistances.

Electrical Stimulation. Battery. Potential. Strength of Current. Resistance.—A muscle-nerve preparation may of course be subjected to the different kinds of stimuli mentioned previously, namely, mechanical, such as may be produced by pricking or pinching; chemical, such as result from contact with sodium chlorid and other agents; thermal, such as may be caused by a heated wire, and electrical. Any one of these influences may be brought to bear upon the muscle directly or through the intervention of its nerve. Under ordinary conditions of experimentation preference is given to the electrical method of stimulation, because it is by far the most convenient, and although the electricity may be produced by a magnet or by friction, the common practice is to derive it from a Voltaic cell.

FIG. 28.—DIAGRAM OF DANIELL CELL.

Cu, copper plate (+); Z, zinc plate (-). The direction of the current is indicated by the arrows.

The place of the generator may be taken by a Daniell, Grove or Léclanche cell. The first consists of a glass jar filled with a concentrated solution of sulphate of copper in which is immersed a round sheet of copper. Inside the latter is a porous earthen cup filled with dilute sulphuric acid in which is contained a rod of zinc. If the outside poles of this cell are now connected by wires, the current leaves at the copper and enters at the zinc. The former pole, therefore, is the positive pole or anode, and the latter, the negative pole or cathode. Inside the cell, of course, conditions are reversed, because in order to complete the circuit the current must flow from the zinc to the copper. The former, therefore, must be positive and the latter negative. A cell of this kind generates a constant electromotive force of about 1.07 volts, but possesses the disadvantage of giving off fumes and acids and requires to be renewed from time to time. These difficulties are not present in the so-called dry cell which is usually a modified type of the Léclanche cell. The latter consists of a glass jar filled with a saturated solution of ammonium chlorid and containing a plate of amalgamated zinc. The inner area of this cell is occupied by a porous cup, containing pieces of carbon and dioxid of manganese. The plate of carbon projecting from this mixture forms the positive pole, while the negative pole is represented by the zinc. The electromotive power of this cell

is 1.5 volts. The ordinary type of dry cell consists of a zinc jacket lined with plaster of Paris and saturated with ammonium chlorid. Its inner space is taken up by a carbon plate surrounded by black oxid of manganese.

While the nature of electricity has not been recognized as yet, we know that an electrical current passes over a system of wires in the same manner as water flows from a high to a low level. It leaves the generator at its place of high electrical *potential* and reenters it at its place of low potential. The point of exit forms the positive pole or anode (ana = up) and the point of entrance, the negative pole, or cathode (cata = down). The difference in the potential between these two points is designated as the *electromotive force*. It is easy to understand that this difference can only be kept up if there is a constant supply of current. As the zinc is being dissolved, the chemical energy liberated thereby tends to maintain a constant electrical pressure at the two poles. The cell, therefore, represents a reservoir of electricity which remains filled as long as there is sufficient material present to generate chemical energy. If, however, the material is used up, the difference in potential can no longer be maintained and an equalization must finally result which causes the current to cease. In this regard electricity behaves like water, because the flow of the latter from a reservoir continues only as long as the outgo is balanced by an adequate ingo.

While traversing a system of wires the electrical current loses a certain amount of its initial energy, owing to the resistance which it must overcome. Hence, the strength of the current or the rate of flow of electricity between two different points of a conductor is dependent not only upon the electromotive force but also upon the resistance resident in the conducting path. Obviously, if the poles of a cell are connected by means of a short and thick wire, the resistance to be overcome will be less than if joined by a long and thin wire. In the former case, therefore, the flow of electricity will be greater than in the latter, provided, of course, that the electromotive force remains unaltered. It must also be evident that the strength of a current through a certain length and thickness of wire must be directly proportional to the electromotive force. In addition to this *external resistance* which the electrical current encounters in its passage through a conductor from copper to zinc, it must also overcome the *internal resistance*, resident in the constituents of the cell between the zinc and copper. Provided that the conducting power of the liquid remains the same, the resistance must decrease with the size of the plates and increase with the distance between them.

Measurement of Electrical Quantities.—In accordance with the metric system, a unit of current is designated as an ampère, a unit of electromotive force as a volt, and a unit of resistance as an ohm. An ohm equals the resistance of a column of mercury 1 mm. in cross-section and 1063 mm. in length at 0°C. The electromotive force or the electrical pressure, so to speak, of a Daniell cell is about one volt. If this power is permitted to act through a resistance of one ohm, a current of approximately one ampère is obtained. In the case of the Daniell cell, however, the amperage is really somewhat smaller, because even if the outside wire possesses a resistance of only one ohm, the total resistance to be overcome by the current is actually greater, owing to the fact that it is also opposed by the internal resistance of the cell. The relationship existing between these different factors has been determined experimentally by G. S. Ohm (1827), in accordance with the following formula:

Current strength = $\frac{\text{electrom. force}}{\text{Int. res.} + \text{Ext. res.}}$ or amperes = $\frac{\text{volts}}{\text{ohms}}$. Since these factors are very closely related, it is possible to determine any

one of them, provided the values of the other two are known. Thus:

$$\begin{aligned}\text{volts} &= \text{amperes} \times \text{ohms} \\ \text{amperes} &= \text{volts} \div \text{ohms} \\ \text{ohms} &= \text{volts} \div \text{amperes}\end{aligned}$$

Polarization.—The two metals of a battery, copper and zinc, are surrounded by electrolytes, the tendency of which is to pass toward the opposite pole. Thus, the positive ions, Cu and H, progress toward the cathode, while the negative OH and SO₄ pass toward the anode which, inside the cell, is the zinc. The copper plate then becomes covered with bubbles of hydrogen which finally place so high a resistance in the path of the current that it is neutralized and ceases to flow. This action which is called polarization, finally leads to the production of secondary currents, the direction of which is opposite to that of the primary one. It may also happen that some of the sulphate of zinc is attacked by the hydrogen and is deposited upon the copper plate in the form of a film of constantly increasing thickness. This action must necessarily lead to a reduction of the electromotive force and finally to a cessation of the primary current. In the Daniell cell, the occurrence of polarization is prevented by the copper sulphate and in the Léclanche cell by the dioxid of manganese.

Under ordinary conditions the electrical current is passed through living substance by means of two copper wires which may be equipped with small platelets of platinum. In order to lessen the resistance, these points of contact should be covered with cotton moistened with saline solution. If applied for a considerable length of time, these metal electrodes become covered with the products of the electrolysis resulting in the course of the passage of the electrical current through this moist conductor, formed by the muscle and nerve tissue. Thus, if a current is conducted through water, a film of bubbles of oxygen eventually accumulates upon the platinum of the positive pole, while the negative pole becomes covered with hydrogen. Presently, the latter assumes a positive change and gives rise to a current which passes in a direction opposite to that of the original current. The final outcome of this is a neutralization of the primary difference in potential. This polarization of the electrodes may be avoided by using so-called non-polarizable electrodes. Those devised by Du-Boid-Raymond consist of zinc terminals immersed in a solution of zinc sulphate. A very simple form may be made by taking two pieces of curved glass tubing, measuring 4 mm. in diameter and about 6 cm. in length. The lower end of each tube is filled with modelling clay or kaolin moistened with normal saline solution. The remaining space in each tube is filled with a satu-

FIG. 29.—NON-POLARIZABLE ELECTRODES.

M, muscle or nerve; *C*, cotton or camel's hair brush; *S*, solution of zinc sulphate; *Z*, amalgamated zinc.

rated solution of sulphate of zinc into which is placed a short rod of amalgamated zinc carrying the end of the copper wire. At their points of contact with the muscle or nerve a small tuft of cotton should be placed which has been thoroughly moistened with saline solution. These electrodes must be carefully washed after each experiment and must always be kept in saline solution for several hours before they are used in order to render the clay completely permeable. Polarization is impossible in this case, because at the junction of the cathodal metallic zinc with the liquid conductor ZnSO_4 , the cation Zn deposits itself upon the zinc electrode and does not act upon the water to liberate hydrogen gas. In quite the same way, the anode is kept free, because there the sulphion SO_4 does not attack the water but the zinc, forming ZnSO_4 .

The Making and Breaking of the Current.—The electrodes are always permitted to remain in contact with the muscle-nerve preparation, while the making and breaking of the current is accomplished

FIG. 30.—THE MAKING AND BREAKING OF THE CURRENT BY MEANS OF A DuBOIS-REYMOND KEY (K).

by the closing and opening of a *key* or switch, interposed between the positive pole of the battery and the positive electrode. The DuBois-Reymond key consists of two bars of brass connected by a rocking plate. If arranged as is shown in figure 30A, the current is made to pass through the muscle by closing this bridge, while its opening breaks the circuit. If arranged as is represented in figure 30B, the bridge remains down to begin with. The current then flows from the anode to the cathode of the battery through the key and does not reach the muscle at all, because the resistance offered by the tissue between the points of contact of the electrodes, is very much greater than that resident in the brass bridge. Conversely, if the key is raised, the current must seek its level by way of the longer course through the muscle, while its closure again permits the current to seek the battery by following the path of least resistance through the brass bridge. By the latter procedure the current is short-circuited.

In many cases it matters little which way this friction key is adjusted. Under certain conditions, however, it is desirable to stimulate while the current is already under way and in closest proximity to the muscle (*B*) rather than that it must first expend a certain amount of its initial energy in passing all the way from the battery to the preparation (*A*). Furthermore, if adjustment *B* is employed, the muscle does not remain in direct connection with the battery, while in *A* it remains in contact with the positive pole as long as the key is kept open. This arrangement may at times give rise to unipolar stimulation. Many other forms of keys have been devised. A

FIG. 31.—POHL COMMUTATOR.

By moving the bridge *B* in the manner here indicated the current may be reversed at the preparation *M*. The cross-bar of the bridge is insulated.

very convenient one has been described by Morse. The current is made by pressing upon a lever which is again forced upward by a spring as soon as it is no longer pressed upon. In the mercury key, contact is made by dipping the pointed end of the bridge into a small porcelain cup filled with mercury.

Commutators or pole-changers, such as have been devised by Pohl, are sometimes inserted in the circuit in order to be able to divert the current alternately into two sets of electrodes and also to reverse its direction. A very useful type of pole changer consists of a round block of wood containing six depressions filled with mercury. The wires from the battery are connected with the two central cups situated upon the opposite sides of the block. These cups contain the supports of a double rocking bridge which may be adjusted in such a way that the current is diverted into the wires leading off from either pair of outside cups, or is reversed by directing it across the central connections (Fig. 31).

Different Types of Current.—If the two poles of a Voltaic battery are connected with one another by wires and a simple key, the current begins to flow as soon as the bridge is closed and ceases to flow as soon as it is opened. Moreover, provided that the electromotive force and the resistance remain the same, the current must retain a definite strength or volume from its make to its break. A current of this kind is characterized as a *constant or galvanic* current. It must be kept in mind, however, that the flow of an electrical current is not identical with that of water through a pipe, but consists merely of a transfer of energy in the form of electricity. The nature of this force is not known.

In 1831, Faraday wound two coils of insulated wire around a ring of iron, the ends of which he connected with a galvanometer. On passing a galvanic current through the iron, he found that the needle of the galvanometer was deflected first on the make and again on the break of this current. This deflection was only of momentary duration, but clearly proved that the primary current also produced a current in the second closed circuit of wires. Peculiarly enough, the secondary current appeared only at the very moment when the battery current was made and broken. He obtained very similar results with coils placed next to one another on wooden cylinders and also with the aid of a magnet surrounded by a coil of wire. A current which is produced in a closed secondary circuit whenever the current flowing through a neighboring primary circuit is made or broken, is called an *induced current*. Inasmuch as this induction may be repeated either at longer intervals or in very rapid succession, we recognize *single* as well as *quickly repeated induction shocks*. The former represent widely separated make and break shocks, while the latter are made to follow one another in such rapid succession that they give rise to an almost constant flow of stimuli. The latter constitute the so-called “tetanic” current.

The Induction Coil.—The induction apparatus devised by DuBois-Reymond, consists of a spiral of about 130 coils of insulated copper wire of medium thickness, the ends of which are connected through a key with the two elements of a battery. These connections form the *primary circuit*. The core inside the primary coil is filled with a bundle of straight pieces of thin iron wire coated with shellac. A second spiral containing about 6000 coils of insulated copper wire of a thickness of 0.1 mm., is placed around the primary coil in such a way that it may be pushed completely over it or farther away from it. The two ends of this secondary coil are continued onward to the electrodes. These connections form the *secondary circuit*.

At the very moment when the primary current is made, a current is also set up for a brief period of time in the secondary circuit. It should be emphasized, however, that this secondary current is merely induced, and is therefore absolutely independent of the primary current. This fact may be made more evident by placing the secondary coil at some distance from the primary so that there is an empty

space between them. A similar induction is developed when the primary current is broken. During the interim, however, there is no induction in spite of the fact that the current in the primary coil continues without interruption.

If the direction of the induced current is now determined by means of a galvanometer, it is found that the making induction shock is opposed to the primary current, while the breaking induction shock possesses the same direction as the primary current. It should also be emphasized that the make induction develops more slowly than the break induction. This difference is due to the fact that the

FIG. 32.—THE INDUCTORIUM (DuBois-Reymond).

A, primary coil; B, secondary coil; P, binding posts for wires from battery; P', binding posts for wires leading to stimulating electrodes. (Howell.)

entering primary current must first of all overcome the *self-induction* of the primary coil before it can produce its characteristic effect in the secondary coil. While it passes from segment to segment of the primary wire, an induced current is momentarily set up in the more distant stretch of wire which pursues a direction opposite to it and tends therefore to lessen its strength. Until this resistance has been overcome, it cannot possibly exert its full energy upon the secondary circuit. On the break, however, this hindrance is not present, so that the induction in the secondary coil can reach its maximum with much greater rapidity. For this reason, the break

FIG. 33.—THE INDUCTORIUM.

I, primary circuit and coil; II, secondary coil and circuit; K, key; J, automatic interrupter; N, nerve.

shock always stimulates living substance more intensely than the make shock. The constant current, on the other hand, stimulates more on the make, *i.e.*, at the time when it first enters the living substance with its initial amplitude.

The strength of the induction shocks depends first of all upon the strength of the primary current and therefore also upon the strength of the battery. In the second place, it is proportional to the distance between the two coils, *i.e.*, it becomes the weaker, the farther the secondary coil is removed from the primary. Thus, we generally estimate the strength of an induction shock by determining the

distance of the coils in centimeters in conjunction with the strength of the cells in volts.¹ It need scarcely be mentioned that the induction may also be diminished by placing the secondary coil at an oblique angle to the primary. When at right angles to one another, the secondary current fails to develop.

The primary current may be made and broken at different intervals, an induction resulting each time. When interrupted very rapidly, the inductions in the secondary circuit follow one another in such quick succession that they are frequently designated as a *faradic* or *tetanic current*. In order to avoid in the latter case the opening and closing of the key with the hand, an interrupter has been provided which automatically makes and breaks the primary current. The one devised by Neef consists of a vibrating steel rod (*V*) and a magnet (*E*). The current

FIG. 34.—THE AUTOMATIC INTERRUPTER OF THE INDUCTORIUM (NEEF'S).

A, entrance of current from battery into post B and vibrator V as far as D. In accordance with the position of the vibrating plate, the current now flows either back to the battery C through post F or into the primary coil PC through D. In the latter case, the current first traverses magnet E before it can reach the battery by way of post F.

from the battery (A) is led into the pillar B as far as the platinum contact (D) upon the vibrator. If the latter is in contact with the end of the wire of the primary coil (PC) at D, the current traverses this spiral and returns to pillar F and the battery (C) by way of a double spiral (E). But as the current passes through spirals E, their iron cores are magnetized and attract the iron plate H of the vibrator, thus breaking the contact of the vibrator at D. The current then flows directly into F and back to the battery (C) by way of contact K. When the primary current is broken in this way, the spirals (E) are again demagnetized. The iron plate (H) being released, the vibrating rod moves upward and again makes contact at D. At the very moment when the primary current is thus made and broken, an induced current is developed in the secondary coil which, however, is not shown in figure 34.

¹ Martin, Am. Jour. of Physiol., xxviii, 1911, 49.

CHAPTER V

PECULIARITIES OF MUSCLE TISSUE

Extensibility and Elasticity of Muscle.—If a rubber band is successively loaded with a number of small weights, it suffers an extension each time. The height of these extensions remains the same throughout this test and is proportional to the load applied. If the weights are then removed one by one, the rubber band again shortens and eventually assumes its original length. If a muscle, such as the gastrocnemius, is successively extended by a limited number of weights of 10 grams each, it is found that the extensions are greatest directly after the application of the weight and then gradually decrease¹

FIG. 35.—EXTENSIBILITY AND ELASTICITY.

A, rubber band and B, gastrocnemius muscle of frog successively loaded with 10 gram weights. The second curve shows a decreasing extension for equal increments, hence, the line joining the end of the ordinates is curved.

(Fig. 35B). But naturally, each weight must be permitted to act for a moderate length of time, because the muscle substance is viscous and yields only slowly to the strain. If the weights are now removed one by one, the muscle again shortens, but does not attain its former length. Its detension, therefore, is imperfect and hence, the excised muscle must be regarded as being incompletely elastic. Its behavior is similar to that of other organic bodies.² While in its normal position in the body, its elastic power is of course absolute, so long as it is not acted upon by excessive weights.

If the weights are added continuously, the elastic power of the muscle is eventually overcome. Beginning at this point, its extension occurs with great rapidity until it tears. In the case of the sartorius muscle, this breaking point lies at 500 grams and in the case of the gastrocnemius at about 750 grams. From these figures it may readily be gathered that the strain which such small masses of muscle

¹ Dreser, *Archiv für Exp. Path. u. Pharm.*, xxvii, 1890, 51.

² Brodie, *Jour. of Anat. and Physiol.*, xxix, 1895, 367; and Hayercroft, *Jour. of Physiol.*, xxxi, 1904, 392.

tissue are capable of withstanding, is astonishingly great. To begin with, therefore, the successive application of these weights gives rise to a curve, the concavity of which is turned toward the abscissa, while eventually, when the elasticity of the muscle has been overcome, it is turned downward. Dead muscle is less extensible than living muscle, whereas contracted or fatigued muscles are more extensible.

The elastic power of muscle tissue serves as a protection against injury by sudden counter forces. Especially in the case of the striated type, it minimizes the possibility of damage to the bones and tendons. Furthermore, this elastic tension prevents the muscles from relaxing completely so that they are always held in a condition of "setting" which enables them to react more promptly as well as more smoothly. It serves, therefore, to conserve the energy which is required to produce a contraction. In many cases, the skeletal muscles are arranged antagonistically to one another, so that the contraction of one set places the others under a certain elastic tension. This is especially true of the flexors and extensors of the arms. Elastic forces also play a most important part in the production of the pressure which is required to drive the blood through the circulatory system. In this particular instance, however, this function is assigned to the elastic tissue of the blood-vessels rather than to the smooth muscle cells. Cardiac muscle exhibits its elastic power most clearly at the beginning of ventricular systole, *i.e.*, directly after the ventricular wall has been fully distended by the forcible emptying of the auricles.

Tonicity of Muscle.—A normal muscle, when resting, is not retained in a condition of complete relaxation, but is held in a state of the slightest possible contraction. The factor which is chiefly responsible for this tonic setting of a muscle is the elastic tension of its constituents. Thus we find that the division of one sciatic nerve causes the corresponding leg to hang down much lower than that of the opposite side, because its muscles have now entered a state of complete relaxation. It should be noted, however, that the tension of the muscles does not constitute the condition of tonus, but is merely one of the prerequisites thereof. Tonus in reality is the result of a continuous influx of impulses from the central nervous system.

In further analysis of this phenomenon it will be found that ganglion cells and their efferent adjuncts retain their function only if allowed to remain in contact with those sense organs which keep them in activity by means of their centripetal impulses. If these impulses are prevented from reaching the center, the corresponding effector becomes inactive and loses its tonus. So it is with muscle. It cannot be said, therefore, that the cells of the spinal cord are automatically concerned with the production of tonus, because their activity, and hence also the tonus of the muscles innervated by them, disappears very promptly after the dorsal roots of the spinal nerves have been divided. It will be remembered that these paths serve as highways for a large number of afferent impulses. Their destruction,

therefore, must give rise to a loss of stimulation and tonus. Afferent impulses may come from the skin and subcutaneous tissue as well as from the muscles themselves; in fact, they may also arise in higher centers. Concerning those arising in the muscles themselves, it may be stated at this time that the division of the afferent path of a muscle, or groups of muscles, is generally followed by a considerable loss of their tonus. It seems, therefore, that the so-called muscle-sense has much to do with this phenomenon. The pressure exerted by the contracting fibers upon the muscle-spindles, sets up certain afferent impulses which are eventually relayed to the effector, and keep the latter in a condition of functional alertness. In last analysis, therefore, the tonus of muscle must be regarded as a reflex phenomenon.

The Trophic State of Muscle.—The anatomical and functional integrity of a muscle can only be retained if it is subjected to frequently repeated stimulations. In case the latter cease at any time, say, in consequence of the severance of the path by means of which the muscle is connected with the central nervous system, it undergoes retrogressive changes and finally loses its functional usefulness entirely. This atrophic state is ushered in by a diminution in its irritability, lasting a number of days. Subsequent to this period its irritability again increases and remains high for several weeks until it is abolished altogether. During the second phase the muscle is prone to exhibit irregular contractions which remain confined to certain groups of its fibers and impart a peculiar fibrillary motion to its substance as a whole. Peculiarly enough, this degeneration may be arrested at any time by reuniting the ends of the cut nerve. The muscle then gradually recovers and regains its normal trophic condition in the course of time. During the interim the muscle may in a measure be prevented from losing its function altogether by stimulating it artificially through the integument.

It must be evident, therefore, that the metabolism of a muscle is absolutely dependent upon its connection with the central nervous system. For this reason, it is commonly held that the ganglion cells exert a trophic influence upon the muscle, which, however, is brought to bear upon it through its ordinary motor nerve and not through special trophic fibers. Hence, any motor nerve may be said to possess trophic qualities, because it keeps the muscle in activity, thereby favoring its metabolic processes. The blood supply is, of course, of some importance, because a copious flushing out of the muscle retards the process of degeneration, while a scanty blood supply greatly favors the occurrence of these changes. This fact is demonstrated in a convincing manner by Stenson's experiment. If the abdominal aorta of a rabbit is ligated, the muscles of the posterior extremity soon lose their irritability, owing to the decrease in the supply of oxygen and other nutritive material. Upon releasing the compression their function reappears very quickly. The same results may be obtained by perfusing them with venous blood or by retarding the flow

until the venous blood has acquired considerable amounts of carbon dioxid.

The Wave of Contraction.—A long muscle generally receives its nerve fibers from a place about midway between its two ends, while a short and compact muscle usually receives them at its upper pole. It is of course essential that its constituent fibers contract at about the same time, otherwise the best mechanical results cannot be obtained. For this reason, the nerve terminals are commonly distributed in such a way that the impulses reach the individual fibers at about the same time and produce, therefore, a contraction which, to all appearances, occurs practically simultaneously throughout the muscle.

It can easily be shown, however, that the contraction of striated muscle starts at the point stimulated and progresses from here to its

FIG. 36.—THE WAVE OF CONTRACTION.

M, sartorius muscle of frog, *A* and *B*, two levers placed horizontally upon muscle; *S*, stimulating electrodes; *T*, time; *K*, kymograph. When stimulated at *S*, lever *A* is raised first.

more distant segments. Thus, if the sartorius muscle of a frog, or one of the long muscles of the neck of a turtle, is placed flat upon a board with two writing levers resting horizontally upon its two ends, a stimulus applied to one of its ends first of all produces a rise of that lever which lies nearest the seat of the stimulation (Fig. 36). No special record of the time need be taken, because the interval between the contractions of the two poles of the muscle is quite apparent even without this. It is advisable, however, to curarize the muscle beforehand so that the wave of excitation cannot be spread by means of the intra-muscular nerve fibers. From this fact it may be deduced that the contraction travels over muscle in the form of a wave possessing a definite velocity. If the distance between the two levers is compared with the difference in the time between the two contractions, the speed with which this wave is propagated, can easily be determined. Ac-

cording to Rollett and Engelmann, it amounts to 3-5 m. per second in cold-blooded animals, and to 6 m. per second in warm-blooded animals. For human muscle the value of 10-13 m. in a second has been given. The removal of the muscle from the body, cooling or fatiguing it, and other factors, tend to diminish the speed of this wave. It is independent of the strength of the stimulus.

Very characteristic progressive contractions of muscle are also exhibited by the stomach, intestine and ureter, but naturally, we are dealing in these cases with smooth muscle which gives the so-called peristaltic wave. This form of contraction is produced by the interaction of the circular and longitudinal fibers, and although regulated by a nervous mechanism in most cases, this regulation is not absolutely essential, as may be gathered from the observation that the upper portion of the ureter contracts with perfect precision although it contains no nervous elements. The same may be said regarding excised segments of arteries. The contraction of the heart is also described as wave-like, the auricles contracting first and the ventricles last, and both in a direction from base to apex. Even excised pieces of cardiac muscle exhibit this wave-like manner of contraction, as may be shown by converting the ventricle of a frog into a zigzag strip by several transverse incisions and stimulating this preparation either at its base or at its apex. The contraction will then be seen to progress from the area stimulated to the opposite end of the strip.

The Muscle Sound.—If a stethoscope is applied over a contracting muscle, such as the biceps, a low rumbling sound is heard,¹ corresponding to a frequency of 30-40 vibrations to the second. A sound is also produced by the contracting masseter muscle which may be rendered audible by placing the side of the face flat against a receiving body or by shutting the ears with the index fingers.² Helmholtz³ has called attention to the fact that this sound corresponds in reality to the resonance sound of the external ear. By determining its pitch with the help of different vibrating reeds held in contact with the contracting muscle, he came to the conclusion that it is chiefly constituted by the first overtone of a sound possessing a frequency of vibration of 18-20 in a second. Two very characteristic sounds are also produced by the contracting ventricle of the heart, of which the first is almost entirely muscular. Even excised pieces of ventricle emit a sound.

¹ Discovered by Wollaston and Erman 90 years ago.

² Stern, Pflüger's Archiv, lxxii, 1900, 34.

³ Wissensch. Abhandl., ii, 928.

CHAPTER VI

THE CHARACTER OF THE CONTRACTION OF MUSCLE

The Simple Twitch.—In accordance with the frequency and character of the stimulus, striated muscle reacts by giving either a simple twitch-like contraction or a prolonged contraction, known as tetanus. The former is obtained whenever the muscle or its motor nerve is excited with a single stimulus, whether it be mechanical, electrical, thermal or chemical. A graphic record of it may be made by connecting the muscle with a writing lever in the manner described previously. If the kymograph is permitted to remain stationary, the contracting muscle registers merely a straight line approaching the

FIG. 37.—A MUSCLE TWITCH.

M, make shock recorded by magnetic signal connected with primary circuit. Time in $\frac{1}{100}$ sec.; *L*, latent period; *C*, period of contraction; *R*, period of relaxation.

vertical, whereas a revolving kymograph will tend to separate the up and down strokes more and more as its speed is increased. The result is a wave-like curve, possessing a certain height and length. A tuning fork, carrying a marker upon one of its prongs, is usually permitted to register its vibrations below the writing lever of the muscle. Moreover, if the electrical method of stimulation is employed, the moment at which the shock is thrown into the muscle or its nerve, may be registered by means of an electro-magnetic signal which is inserted in the primary circuit and is permitted to write in the same ordinate as the other levers.

If a muscle-curve of this kind is studied in detail, it is seen to consist of two principal phases, namely a *period of contraction* and a *period of relaxation*. During the former the muscle shortens until it has attained its state of maximal contraction, while during the latter it relaxes until it has again reached its natural length and form. If a comparison is now made between this curve and the record of the signal

and that of the tuning-fork, it will be found that the muscle does not begin to contract precisely when the shock is passed into it, but a moment thereafter. This period, intervening between the application of the stimulus and the reaction, is designated as the *latent period*. Hence, a muscle curve really presents three phases, namely a latent period, a period of contraction and a period of relaxation. No visible mechanical energy is liberated during the first, because it is occupied solely by various changes anteceding the actual contraction.

If the indirect method of stimulation is employed, it may be thought that a large part of the latent period is consumed in the passage of the nerve impulse to the muscle. This contention, however, cannot be considered of much value, because the shifting of the electrodes to a place very close to the muscle does not materially shorten this interval, nor does their removal to a more distant point give rise to an appreciable lengthening. It must be evident, therefore, that the conduction of the impulse over the nerve consumes only the briefest possible time and that by far the greatest part of the latent period is consumed in initiating those changes which finally bring the mechanism of contraction into play.

As far as the time relationship between these periods is concerned, it should be stated first of all that the duration of a simple contraction of muscle is subject to certain variations which depend upon the character of the muscle tissue and its condition at the time of experimentation.¹ A perfectly fresh gastrocnemius muscle of the frog completes its contraction in about 0.1 sec., of which 0.01 sec. is taken up by the latent period, 0.04 sec. by the contraction and 0.05 sec. by the relaxation.

Summation and Fusion of Contractions.—If a second shock is sent into the muscle very shortly after the beginning of its relaxation following the first stimulus, a second contraction will be obtained which is higher than the first. This phenomenon is known as *summation of contractions*. In quite the same manner, a third contraction may be added to the second and a fourth to the third, and so on, until the relaxations intervening between them become very incomplete and the individual contractions are fused into an *incomplete tetanus*. If the individual stimuli are now permitted to succeed one another so rapidly that the relaxations cease to be discernible and the curve as a whole pursues a straight course, the muscle records what is commonly described as a *tetanus*.

It should be remembered, however, that the interval between the succeeding shocks cannot be shortened indefinitely, because a point will eventually be reached when the second stimulus loses its effectiveness. This fact implies that a certain period must always be allowed to intervene between the different stimulations, otherwise the muscle will be in no condition to receive the succeeding stimulus. In

¹ Schultz, Archiv für Anat. und Physiol., 1897,* 22; also see: C. C. Stewart, Am. Jour. of Physiol., iv, 1901, 202.

other words, the destruction of the myoplasmic material must first be made good by anabolic changes before the muscle can again respond. This period during which the muscle remains inexcitable to a second stimulus, is known as the *refractory period*. Its duration is only about 0.0015 sec. Thus, a muscle is in a position to react to stimuli only if

FIG. 38.—SUMMATION OF CONTRACTIONS.

M and *B*, make and break shocks indicated by an electro-magnetic signal. Time in $\frac{1}{100}$ sec. As the break contraction occurs during the period of relaxation of the make contraction, it is added to the first.

they recur with a lesser frequency than one in every 0.0015 sec. If their rate is increased beyond this limit, not every stimulus will be capable of producing a reaction. As will be shown later, the refractory period is of especial functional significance in the case of cardiac muscle.

FIG. 39.—FUSION AND TETANUS.

S, summation; *F*, fusion; *T*, tetanus. Time in seconds. The individual make and break shocks are repeated so quickly that a continuous contraction is obtained.

Tetanus.—A tetanic contraction of muscle exhibits a greater height and length than the simple twitch. It must be evident from the preceding discussion that a tetanus is really composed of a multitude of single contractions which have been fused into a continuous curve by permitting the stimuli to enter the muscle at very brief in-

tervals. Hence, the height of a tetanic contraction must always exceed that of a twitch and its summit must be attained more quickly, provided, of course, that the same strength of stimulus is employed in both cases. Having reached its maximal degree of shortening, the muscle remains in the contracted condition until the stimuli are made to cease. It need not surprise us, however, to find that the continued activity of the muscle leads to a destruction of material which eventually causes it to become fatigued. This phenomenon is indicated in the curve by a gradual decline of the lever which becomes the greater, the longer the duration of the stimulation. Eventually, therefore, the muscle must return into the position of complete relaxation in spite of the continuance of the stimulation. Under ordinary conditions, however, the stimuli are sent into a muscle only for a relatively short period of time, but naturally, even the briefest tetanus is longer than a simple twitch.

FIG. 40.—TETANIC CONTRACTION.

Recorded by means of Neef's automatic interrupter. Time in seconds. The decline of the curve is an indication of fatigue.

Whether or no a muscle will become greatly fatigued depends, of course, upon its condition at the time of experimentation and upon the strength and duration of the stimulation. Thus, an already somewhat fatigued muscle requires a much smaller number of stimuli to be tetanized than one just freshly prepared. The same is true of a cooled muscle as against one which is kept at the temperature of the room. It is evident, therefore, that the number of stimuli which are necessary to tetanize a muscle completely, differ very widely. Ordinarily a frog's gastrocnemius necessitates about 20–30 in a second, and smooth muscle one in every 5–7 seconds.

Voluntary Contractions.—Inasmuch as our skeletal muscles contract normally in consequence of an influx of stimuli from the cerebral cortex, their reactions may be of almost any length, until they are finally cut short by fatigue. We have seen that a frog's gastrocnemius completes its contraction in about 0.1 second. Contractions of such brevity are not given by mammalian muscles, because even such seemingly instantaneous movements as the closure of the eyelids or the trilling motion of the fingers, cannot be executed in a shorter time

than 0.5–1.0 second. In accordance with this result, it is generally believed that our voluntary contractions bear a close resemblance to the tetanus of excised muscle. This would imply that even our briefest muscular movements are the result of a series of stimuli sent into the muscle at regular intervals during the continuance of its contraction. From this it may be inferred in turn that even the shortest contractions of our muscles are composed of a number of simple twitches. This inference is strengthened by the observation that a contracting muscle emits a sound which possesses a vibration frequency of 30–40 in a second. This discontinuity of the contractions of our skeletal muscles is indicated further by the curve recorded by our fingers when held in voluntary tetanus. When registered upon a slowly revolving drum, this curve invariably exhibits irregular oscillations, such as occur in the course of general spasms of the musculature resulting from irritations of the central ganglion cells. Quite similarly it has been shown by Piper¹ that if a string-galvanometer is applied to the flexor muscles of the forearm, the stimulation of the median nerve elicits a typical diphasic deflection of the needle. It was also found that the voluntary contraction of these muscles gives rise to about 40 or 50 of these diphasic variations in the course of a second. Other muscles gave similar results. By connecting this instrument with the phrenic nerve, Dittler has proved that the diaphragm may be contracted by a discharge of impulses possessing a frequency of 50 to 70 in a second.

These results indicate very clearly that a muscle does not contract in consequence of the influx of a single stimulus, but in consequence of a series of stimuli. It must be evident, therefore, that the motor cells innervating a muscle always discharge a series of impulses which give rise to a serial evolution of muscular energy. Their discontinuance then permits the relaxation to set in. The analogy between a voluntary contraction and one produced in excised muscle by artificial stimuli, is therefore a very close one. These statements may also be applied to the tonus of muscle, with this modification, however, that the stimuli upon which the tonic condition of muscle tissue depends, are of subminimal intensity. These rhythmic discharges by the central ganglion cells give rise to a discontinuous evolution of energy which just suffices to keep the muscle in a semi-active condition, ready to respond to any supraminimal stimuli that may impinge upon its neuromuscular junction.

Contracture.—The term contracture signifies that the relaxation of the previously contracted muscle is unduly prolonged, or, as may also be said, that its contraction is maintained for an abnormally long time. This condition is frequently encountered during fatigue, or when a fresh muscle is cooled or is subjected to excessive stimulation. It may also be produced in a chemical way by the administration of small doses of veratrin or barium, and, in a lesser degree, also by

¹ Pfüger's Archiv, cxix, 1907, 301, and Archiv für Physiol., 1914, 345.

strontium and calcium. It is frequently associated with lesions of the central nervous system, such as give rise to hemiplegia. It may also appear as a functional disorder in somnambulism and hysteria; in fact, if these conditions have persisted for sometime, it may happen that entire groups of muscles remain permanently in an exaggerated tonic or contracted state. Unless degenerated, muscles of this kind may still be made to give either short twitches or tetani. This fact tends to show that an ordinary contracture is different from a tetanus. It represents merely a tonic setting or contraction of the muscle in consequence of an intrinsic or extrinsic excitation and may be classified either as functional or organic, in accordance with its cause and duration.

Explanations of this phenomenon have been submitted by Fick, Grützner and von Frey. More recently Botazzi¹ has stated that a contracture represents merely an exaggerated condition of tonus

FIG. 41.—CONTRACTURE OF MUSCLE.

A, contracture; B, tonic contracture; C, clonic contracture.

which serves as an "internal support" to the muscle. It is a well known fact that tonus varies negatively as well as positively. Hence, if a muscle is stimulated while maintaining its shortened condition, the resulting contraction rises above the level of the contracture, but the quick shortening observed at this time is independent of the slow persistent shortening causing the contracture. It is believed by Botazzi that the former is made possible by the activity of the anisotropic substance, and the latter by that of the isotropic substance.

Under certain conditions, and especially during irritations of the central nervous system, these prolonged tonic contractions frequently assume a rhythmic character. They are then designated as *clonic contractions*. A brief clonus of certain muscles is often obtained in neurasthenia and hysteria. A very typical one may be produced in certain cases of organic disease of the spinal cord by suddenly flexing the foot upon the leg. This abrupt stretching of the calf muscles causes them to contract rhythmically for some time, thus giving rise to the so-called ankle-clonus.

¹ Jour. of Physiol., xxi, 1897, 1.

CHAPTER VII

THE FACTORS VARYING THE CHARACTER OF THE CONTRACTION

The Strength of the Stimulus.—In general it may be stated that the height of the contraction is proportional to the strength of the stimulus. A very convenient way of illustrating this rule is to permit a muscle to record its contractions upon a stationary drum while being stimulated with single make or break induction shocks. By varying the distance between the secondary and primary coils of the inductorium the strength of these stimuli may be accurately graded. If this experiment is begun with the coils far apart, no contractions are obtained at first, although it may be surmised that the different stimuli then give rise to certain chemico-physical alterations in the

FIG. 42.—SUCCESSIVE MAKE AND BREAK CONTRACTIONS.

The strength of the current is gradually diminished by more widely separating the secondary from the primary coil. The figures indicate this separation in centimeters of distance. *M*, threshold of make; *B*, threshold of break.

muscle which, however, are still too weak to produce visible mechanical energy. These stimuli are said to be *subminimal* in character. If a number of these subminimal stimuli are passed into the muscle in quick succession, they eventually give rise to a contraction. This phenomenon is known as *summation of subminimal stimuli*.

If the strength of the current is now gradually increased by bringing the coils closer together, a point will finally be reached when the muscle gives a just barely perceptible reaction. This is the *threshold* contraction. Moreover, since the break induction shock constitutes a stronger stimulus than the make shock (page 63), the first contraction must appear when the current is interrupted. If the strength of the current is increased still further, these break contractions gradually increase in height and become associated with the first make contraction. Additional increases in the strength of the current lead to the production of the highest possible contractions, beyond which point their height generally decreases somewhat. Beginning with the thresh-

old, these contractions are designated respectively as *minimal*, *maximal* and *supramaximal*.

The Duration of the Stimulus.—In a general way it may be said that the highest contraction is obtained when the stimulus is of long duration, but this rule is applicable only to stimuli of equal intensity and moderate duration. It is evident that an undue prolongation of the excitation must tend to produce fatigue and to lessen the amplitude of the reaction, until it finally becomes smaller than the one obtained previously with stimuli of much briefer duration.

FIG. 43.—INFLUENCE OF LOAD.

This muscle has been successively loaded with 10 gram weights.

Influence of Load.—Provided that the writing lever has been properly counterpoised so that weights may be attached to it without stretching the muscle, the amplitude of the contractions decreases gradually with the increasing load. It is true, however, that a muscle reacts much better when moderately weighted than when no weight is attached to it at all. In other words, the contractility of a muscle may be augmented by subjecting it to a slight tension.

FIG. 44.—THE CONTRACTION OF FOUR DIFFERENT MUSCLES OF THE TURTLE RECORDED UNDER SIMILAR CONDITIONS.

1, Palmaris; 2, Gracilis; 3, Omohyoid; 4, Pectoralis Major.

Character of the Muscle Substance.—We have previously seen that the irritability, conductivity, and contractility of muscle tissue differ not only in different animals, but also in muscles of the same animal. Thus, the striated muscles attached to the wings of insects, contract at the rate of 300 times in a second, while those of birds may attain a frequency of 100 in a second. The gastrocnemius muscle of the frog requires 0.1 sec., the hypoglossal muscle of the turtle 0.2–0.3 sec., and those used in the retraction of the head of this animal 0.5 sec.

Similar differences are exhibited by the red and pale muscles of the rabbit, the soleus (red) contracting in 1.0 sec. and the gastrocnemius (pale) in 0.2 sec. In winter the reaction-time of the muscles of cold-blooded animals is much prolonged. Smooth muscle reacts very sluggishly, an ordinary contraction requiring as a rule from 10–20 sec. for its completion.

It is evident, therefore, that muscle tissue differs in its speed of reaction and that this difference is dependent upon chemico-physical peculiarities of its substance. We know that red muscle is a more concentrated tissue than pale muscle and that it embraces a larger amount of sarcoplasmic material. It seems, therefore, that the greater water content of the latter exerts a favorable influence upon its rapidity of action. The same holds true in the case of non-striated and striated muscle. Inasmuch as the latter contains more water and a smaller amount of undifferentiated sarcoplasm, its speed of contraction must be much greater.

FIG. 45.—EFFECT OF CHANGES IN TEMPERATURE ON MUSCULAR CONTRACTION.
The temperature was raised 5° each time.

Influence of Temperature.—Warmth increases the power and speed of reaction of this tissue, because it exerts a favorable influence upon the chemical processes underlying muscular contraction. Hence, a series of myograms recorded at gradually rising temperatures, usually shows a progressive increase in the height and corresponding decrease in the length of the different contractions.¹ At 0° C., or rather, a little below this point,² the muscles of the frog lose their irritability entirely. Consequently, if a muscle of this kind is stimulated at a degree or two above freezing, it gives solely a very low and prolonged contraction. If the temperature is now raised, say, three degrees at a time, the individual contractions decrease in length but increase in height. Beginning at about 9° C., their height is slightly decreased, but again increased at about 18° C. A second maximum is reached at 30° C. Subsequent to this point they again diminish in size until

¹ Gad and Heymans, *Archiv für Physiol.*, 1890, 59.

at about 37° C. the muscle begins to lose its irritability and to pass, at about 40°–42° C., into the condition of heat rigor. Regarding the cause of these variations little can be said; in fact, it has been stated repeatedly that these fluctuations are not altogether constant. It must be concluded, however, that muscle tissue requires a certain optimum temperature which allows it to give reactions of maximal amplitude. For the warm-blooded animals the most favorable temperature is 37° C., and for the cold-blooded animals, the temperature of the medium in which they are living.

Heat rigor, or rigor caloridis, is a permanent condition, corresponding in a way to the coagulation of egg albumin. When entering this state, the muscle gradually shortens and becomes firm to the touch and opaque in its appearance. These characteristics it retains. When placed under a greater tension than 15–20 grams per gram millimeter of substance, it ruptures abruptly.

Effect of Drugs and Chemicals.—Certain chemicals affect the irritability and contractility of muscle in a very characteristic manner.

FIG. 46.—THE EFFECT OF VERATRIN ON MUSCULAR CONTRACTION.

This is especially true of veratrin. A few drops of a 1.0 per cent. solution of its acetate, injected into the dorsal lymph sac of a frog, generally suffice to produce its characteristic effect. The muscle may also be immersed in a solution containing 1 part of the alkaloid to 100,000 parts of a 0.7 per cent. solution of sodium chlorid.¹ By this means a simple twitch of the gastrocnemius may be made to last 50–60 sec., instead of the normal 0.1 sec. Thus, the peculiarities presented by a veratrinized muscle, consist in a surprisingly long period of relaxation which usually presents two summits. It frequently happens, however, that a second stimulus sent into the muscle shortly after it has completed one of these prolonged contractions, again results in a very rapid twitch. If the muscle is then allowed to rest, the succeeding excitation may again produce a long drawn-out contraction. Biedermann has stated that these peculiar effects are dependent upon a dissociation of the red and pale fibers of the muscle. Carvalho and Weiss,² however, have observed the same behavior in muscles which are composed exclusively of either type of fibers; hence, it is quite im-

¹ Buchanan, *Jour. of Physiol.*, xxv, 1899, 137.

² *Jour. de la Physiol. et de la path. gén.*, 1899.

possible at this time to assign a definite cause to this reaction. Barium salts, glycerin, and nicotin produce somewhat similar effects.¹

If a muscle is placed in a 0.6 per cent. solution of sodium chlorid or is frequently moistened with it, it retains its functional qualities for a long time, because this fluid is practically isotonic to the myoplasm. A strong solution of this salt, on the other hand, causes the muscle to twitch irregularly, either as a whole or along certain of its strands of fibers. The muscle then exhibits a behavior very similar to that shown by the fibrillating heart. Inasmuch as these results are also obtained with sodium chlorid dissolved in distilled water, the ordinary preservative fluid for muscle should be made with tap-water which contains at least a trace of calcium. This salt neutralizes the excitatory action of the sodium. More pronounced stimulating effects may be obtained with solutions of Na_2CO_3 , or with a solution containing 0.5 per cent. NaCl , 0.2 per cent. NaHPO_4 and 0.04 per cent. Na_2CO_3 (Biedermann). When mixed in this proportion, these salts are capable of inducing an almost rhythmic activity of skeletal muscle. Potassium salts act as depressants. Thus, even normal saline solution when mixed with a few drops of potassium, will induce fatigue within a very short time. Owing to this fact and because the ash of muscle contains a considerable amount of potassium, it has been thought that the liberation of these salts during muscular activity is responsible for the phenomena of fatigue.

Fatigue.—If a fresh muscle is stimulated for some time with induction shocks of moderate strength, the successive contractions gradually decrease in height but increase in length. Furthermore, if a record is made of the latent period, it will be found that its length is steadily increased, indicating thereby a very definite diminution in the irritability of the muscle substance. This observation may also be made upon a muscle which is subjected to a quickly interrupted current of long duration. The height of the contraction decreases gradually as the current is continued. Quite similarly, it will be noted that the repeated tetanization of a muscle gives rise to curves of slowly decreasing amplitude.

Inside the body, a muscle cannot be fatigued so easily, because its waste products are constantly removed by the blood stream, while new substances are brought to it to replace those which have been lost during the preceding contractions. An excised muscle, on the other hand, possesses only a small store of reserve material and has no means of ridding itself of the fatigue substances. For this reason, it shows these phenomena more promptly and never recovers completely from the stimulations. Its condition, however, may be materially improved by perfusing it with defibrinated blood or normal saline solution. Contrariwise, it is possible to hasten its exhaustion by perfusing it with a dilute solution of lactic acid, or with saline containing a considerable amount of carbon dioxid. These two agents,

¹ Motinsky and Straub, Arch. für exp. Path. u. Pharm., li, 1904, 310.

together with monopotassium phosphate and certain toxins, are said to be responsible for the development of fatigue in muscle. They are spoken of collectively as the fatigue substances.

The phenomena of fatigue are also exhibited by human muscle when subjected to excessive stimulation. We then become cognizant of a peculiar strained feeling and eventually also of pain which prevents us from continuing these efforts. It appears that these sensations are the direct result of an irritation of the muscle-spindles and of the cor-

FIG. 47.—FATIGUE OF MUSCLE.

A gastrocnemius muscle of the frog stimulated successively 150 times. The 1st, 50th, 100th, and 150th contractions are recorded.

responding receptors in the tendons and joints. Under ordinary conditions the tests upon human muscles require the use of an instrument, which is known as the *ergograph*. The one devised by Mosso¹ consists of a support for the arm and a weight which acts in a sliding path or across a pulley and is connected with the tip of one of the fingers, preferably the index finger of the right hand. A spring ergograph, or dynamograph, has been devised by Waller. It consists of a strong

FIG. 48.—FATIGUE CURVES OF FROG'S MUSCLE. (Waller.)

oval steel spring which is compressed by the hand, while a pointer is moved across a graduated scale to indicate the degree of compression as well as the power of the group of muscles used in this act. In either method, the displacement of the weight or of the spring may be registered upon a kymograph by means of a writing lever, the resulting record being known as an *ergogram*.

The fatigue of human muscle may be illustrated either by recording a series of voluntary twitches or a long-continued tetanus of, say, the musc.

¹ Arch. ital. de biologie, xiii, 1890; also see: Treves, *ibid.*, xxix, xxx, and xxxi, 1898-1900, and Schenck, *Pflüger's Archiv*, lxxxii, 1902.

flexor digitorum sublimis, or of the musc. abductor indicis.¹ The former type of contraction, however, must be repeated in rapid suc-

FIG. 49.—Mosso's ERGOGRAPH.

c, is the carriage moving to and fro on runners by means of the cord d, which passes from the carriage to a holder attached to the last two phalanges of the middle finger (the adjoining fingers are held in place by clamps); p, the writing point of the carriage, c, which makes the record of its movements on the kymograph; w, the weight to be lifted. (Howell.)

FIG. 50.—NORMAL FATIGUE CURVE OF THE FLEXORS OF THE MIDDLE FINGER OF RIGHT HAND.

Weight 3 kilograms, contractions at intervals of two seconds. (Maggiara.)

cession, because even a load of as much as 6 kg. lifted at intervals of

¹ Storey, Am. Jour. of Physiol., viii, 1903, 355.

10 seconds, may not be able to induce fatigue. It is also essential to use maximal weights, because the effects of small weights are generally compensated for within a very short time. The interval which should elapse between two successive ergograms showing complete normal fatigue, is close to 2 hours. If a muscle is made to contract before it has fully recovered from a preceding exertion, it may be more severely injured than if it had been forced to lift excessive loads to begin with. Practically no two ergograms are alike, because every person presents certain individual peculiarities which are dependent upon his physiological condition. Thus, pronounced mental or bodily fatigue from such causes as loss of sleep, anemia, lowered nutrition, etc., is prone to produce a more rapid exhaustion of the muscle than could possibly be obtained in a perfectly robust person. Practice and training enhance the power of a muscle, and this end may also be attained by augmenting the local or general circulation by drugs, massage, baths as well as by the ingestion of certain foods, such as sugar.

CHAPTER VIII

THE CHARACTER OF THE CONTRACTION OF SMOOTH MUSCLE

The Tonicity of Smooth Muscle.—The organs and structures containing non-striated muscle cells are innervated by the autonomic system and are therefore not under the direct control of the will. In fact, they are in a way independent of the cerebro-spinal system, because their function continues even after they have been separated from it. Herein lies the implication that they are well equipped with intrinsic nervous elements which are capable of controlling their action even in the absence of the higher centers. If the bladder or a segment of the stomach or intestine is excised and suspended in a chamber under proper conditions of moisture and temperature, it may easily be observed that it retains its tonus and even executes spontaneous contractions. The latter may be of myogenic or neurogenic origin, although Schultz¹ claims that they arise solely in consequence of excitations of local nervous elements and are therefore reflex in their character. In accordance with this statement, the ordinary condition of tonus of non-striated muscle may be said to have both a myogenic and neurogenic cause, the former giving rise to the ordinary elastic state of its substance, and the latter to periodic excitations which are relayed to it by way of definite reflex paths. Considered in this light, the spontaneous contractions of smooth muscle are mere variations in the neurogenic tonus.

¹ Archiv für Physiol., Suppl., 1903. 1; also see: Grützner, Ergebnisse der Physiol., iii, 1904, 2.

The Character of the Contraction.—Even the most casual observation of the peristaltic wave of the stomach, intestine or ureter must show that smooth muscle reacts in a very sluggish manner, but it would be going too far to state that its irritability is less than that of striated tissue. Practically all the different types of stimuli are effective; in fact, in the case of the iris of the eye of frogs and other animals it is possible to produce constrictor reactions even with light.¹ Obviously, this phenomenon cannot be explained by saying that it is due to reflex causes, because the same results may be obtained with small pieces of excised iris. It is also evident that smooth muscle is very susceptible to mechanical and thermal stimuli, but rather insensitive to electrical stimuli. The latter peculiarity necessitates the use of somewhat stronger induction shocks than are ordinarily required to activate striated muscle.

Different types of smooth muscle differ in their speed of reaction, but, broadly speaking, it may be said that their latent period is from

FIG. 51.—CONTRACTION OF SMOOTH MUSCLE (CAT'S BLADDER.)

L, latent period; C, period of contraction; R, period of relaxation; time in seconds.

100 to 500 times as long as that of striated muscle. But inasmuch as the amplitude of the reaction of smooth muscle is directly proportional to the strength of the stimulus, it forms no exception to the general law and gives, therefore, an ascending series of minimal and maximal contractions which increase with the strength of the current.

The chief peculiarity of the curve of contraction of smooth muscle is its great length. Thus, if a preparation of the frog's stomach, the bladder of a cat,² or a segment of intestine is stimulated with a current of moderate strength, minutes usually elapse before it again regains its normal form. In the case of striated muscle, on the other hand, the same quality of stimulus evokes a contraction which is generally completed in less than a second. This difference is dependent upon the fact that the periods of contraction and relaxation of plain muscle are greatly prolonged, so that the entire curve really acquires the characteristics of a contracture of striped muscle. Inasmuch as its shortening is always accomplished in a much briefer time (10–15 sec.) than its relaxation (60 sec.), it is claimed by Winkler³ that the strength of

¹ Guth, Pfüger's Archiv, lxxxv, 1901, 118.

² C. C. Stewart, Am. Jour. of Physiol., iv, 1900, 185.

³ Pfüger's Archiv, lxxi, 1898, 386.

the stimulus required to cause it to contract, must always be great enough to produce a contracture-like effect. Smooth muscle may also be made to show the phenomenon of summation by stimulating it again very soon after it has entered upon its period of relaxation. This summation may be repeated until its maximal degree of shortening has been obtained which, according to Schultz, is frequently 73 per cent. above its resting position or abscissa.

The character of the contraction of *cardiac muscle* will be discussed in a later chapter dealing with the dynamic importance of the heart. It may be stated at this time, however, that its contraction is intermediate between those of striated and non-striated muscle, and is most closely allied to the simple twitch of the former. Moreover, cardiac muscle does not react intermittently, but possesses an automatic power which makes it contract rhythmically in consequence of the generation of certain internal stimuli.

CHAPTER IX

THE CHEMISTRY OF MUSCLE

General Composition.¹—Inasmuch as the muscle tissue of an adult constitutes about 42 per cent. of the body weight, it forms a very considerable part of the total mass of our body. It is also very important functionally, because it produces nearly 50 per cent. of the total metabolism in persons at rest, and almost 75 per cent. in persons undergoing moderate activity. In analyzing muscle tissue, it must be taken into account that it embraces a certain amount of connective tissue and also blood-vessels and nerves. Its principal element is, of course, the fiber which is composed of a contractile albuminous substance or sarcoplasm, and an elastin-like investment, or sarcolemma. The former possesses a semifluid or jelly-like consistency and displays a series of doubly refracting elements. The striated and non-striated types of mammalian muscle contain from 72 to 78 per cent. of water and from 22 to 28 per cent. of solids, the latter being composed largely of proteins.

Proteins of Muscle.—The fact that muscles become perfectly rigid after death as well as on exposure to heat, has led to the belief that their albuminous constituents undergo a process of coagulation similar to that exhibited by the blood of the warm-blooded animals. Thus, Kühne² has succeeded in isolating from them a liquid by first freezing them and then subjecting them to a high pressure. This so-called muscle-plasma clots almost immediately when slightly warmed. The remaining portion of the muscle substance forms the so-called *stroma*. Under ordinary conditions it suffices to divide the muscle into small pieces and to subject

¹ v. Fürth, Oppenheimer's Handb. der Biochemie, Jena, 1910.

² Unters. über das Protoplasma, Leipzig, 1864.

them to a pressure of from 250–300 atmospheres. About 60 per cent. of the weight of the muscle is then obtained as *plasma*.

The Proteins of the Plasma.—Halliburton,¹ has shown that muscle-plasma contains two coagulable proteins, namely myosin and myogen which upon coagulation are transformed into myosinfibrin and myogenfibrin. But this transformation does not seem to be a direct one, because, in the case of myogen, v. Fürth has found an intermediary product which he has called soluble myogenfibrin. This author also calls attention to the fact that the coagulation of muscle-plasma is not strictly comparable to the coagulation of blood, as has been held by Kühne and Halliburton, because the clot is floccular and forms as a rule very slowly. Furthermore, while fresh muscle-plasma is neutral or slightly alkaline in reaction, it becomes distinctly acid after coagulation has set in. This acidity is due to the formation of sarcolactic acid. The serum formed in the course of this process, contains the soluble constituents of muscle.

The Proteins of the Stroma.—The residue left over after the plasma has been squeezed out, consists chiefly of connective tissue, sarcolemma and nuclei. By preventing as much as possible the occurrence of rigor in the excised muscles, Saxl² has found that only a small portion of their total mass consists of stroma. He also states that the plasma proteins in skeletal muscle amount to seven-eighths of the total protein content, while their relationship in cardiac muscle³ is as $\frac{1}{3} : \frac{2}{3}$ and in smooth muscle as $\frac{1}{4} : \frac{3}{4}$. The stroma contains phosphorus which is held in the nucleoprotein. It also embraces phospholipins in combination with the proteins.

Lipins of Muscle.—The fat of muscle is contained chiefly in the connective tissue between its different bundles, but a certain amount of it is also held in the cells themselves. On analysis the former in all probability gives rise to neutral fat, while the latter yields cholesterol and phospholipins. The proportion of these bodies differs greatly in different types of muscle tissue. In skeletal muscle, they may amount to as much as 30 per cent., and in cardiac muscle to as much as 60 or 70 per cent. of the total lipins.⁴ Cardiac tissue is characterized by a large percentage of cuorin which is a monoamidodiphosphatide.

Carbohydrates of Muscle.⁵—The presence of glycogen in muscle tissue was recognized soon after the discovery of this substance by Claude Bernard. It may be present in considerable amounts, namely 1.0 per cent. in the muscles of the cat, 0.4–0.7 per cent. in those of man, and as much as 3.7 per cent. in those of the dog. It seems to be derived from the sugar of the blood, muscle tissue possessing the power of converting the monosaccharide dextrose by dehydration and condensation into the polysaccharide glycogen. The following formula may serve to illustrate this reaction:

Glycogen is stored in the muscle tissue and forms an important nutritive material. For this reason, it must be a constant constituent of all well-nourished resting muscles.

Inorganic Constituents.—Muscle tissue contains a number of salts such as the chlorides, sulphates and phosphates of sodium, potassium, calcium, magnesium and iron, but its chief characteristic is its large content in potassium and phosphoric acid.⁶ The total amount of phosphorus is 0.2 per cent., it being present chiefly in an inorganic form. Ox muscle, for example, contains 81 per cent. of inorganic and 19 per cent. of organic phosphorus, while heart muscle embraces

¹ Jour. of Physiol., viii, 1888, 133.

² Hofmeister's Beiträge, ix, 1906, 1.

³ Lederer and Stotte, Biochem. Zeitschr., xxxv, 1910, 108.

⁴ Erlandson, Zeitschr. für phys. Chemie, li, 1907, 71.

⁵ v. Fürth, Ergebn. der Physiol., Bioch., ii, 1903, 580.

⁶ Urano, Zeitschr. für Biol., l, 1907, 212.

40 per cent. of the former and 60 per cent. of the latter. By far the greatest amount of organic phosphorus is present in the form of phosphatide.

Lactic Acid.—Most generally muscle tissue also contains a certain amount of ethidene lactic acid or sarcosolactic acid, $\text{CH}_3\text{CHOHCOOH}$. This acid is a product of tissue metabolism. It is dextrorotary, while that contained in sour milk, is inactive to polarized light and finds its origin in bacterial fermentations. In normal resting muscle it is difficult to detect it, because it is oxidized as rapidly as it is formed, but its removal may be greatly interfered with by restricting the entrance of oxygen. The amount of this acid is greatly augmented during muscular activity.

Extractives.—If muscle tissue is extracted with boiling water, a number of substances are obtained which are of especial interest, because they represent in all probability the products of the metabolism of muscle. Chief among these are those of nitrogenous origin, because they give rise to some of the substances excreted in urine. As a rule, fresh muscle yields about 2 per cent. of its weight in extractives of which 0.7 per cent. is of organic and 1.3 per cent. of inorganic origin. The one present in largest amounts is *creatin*, $\text{C}_4\text{H}_9\text{N}_3\text{O}_2$, which equals 0.1 to 0.4 per cent. of the weight of the mammalian muscle. *Creatinin*, $\text{C}_4\text{H}_7\text{N}_3\text{O}$, is present in much smaller amounts, but constitutes 0.3 per cent. of the weight of the muscles of fish. No definite conclusions have been reached as yet regarding the origin of these bodies and even the statement of Liebig and Ranke,¹ that creatin is a fatigue substance and increases with muscular activity, has not been substantiated by the more recent and more exact quantitative determinations of these substances.² Carnosin,³ $\text{C}_9\text{H}_{14}\text{N}_4\text{O}_5$, is a basic extractive and is said to be derived from histidin, because on hydrolysis it yields histidin and β -alanin. It is present in about the same proportion as creatin. Other bodies are *carnitin*, *novain* and *taurin*.

The *purins* of muscle are relatively scanty in amount, because by far the greatest part of the muscle cell is composed of cytoplasm. They are represented by such bodies as uric acid ($\text{C}_5\text{H}_4\text{N}_4\text{O}_3$), xanthin ($\text{C}_5\text{H}_4\text{N}_4\text{O}_2$), hypoxanthin ($\text{C}_5\text{H}_4\text{N}_4\text{O}$), guanin ($\text{C}_5\text{H}_5\text{N}_5\text{O}$), adenin ($\text{C}_5\text{H}_5\text{N}_5$) and carnin ($\text{C}_7\text{H}_8\text{N}_4\text{O}_3$). Urea is present in very small amounts in the muscles of mammals (0.04 to 0.08 per cent.), but in much larger quantities in the muscles of certain fish (1 to 2 per cent.).

Pigments and Enzymes.—The red color of muscle is said to be due to a pigment which is known as myohematin or myochrome. Inasmuch as this body presents several of the characteristics of hemoglobin, it is commonly said to be identical with it. Its chief function is respiratory, because it furnishes the muscle with oxygen which it holds in loose combination.

The substances furnished to the muscles by the blood, are made available for their metabolism by hydrolysis, oxidation, reduction and synthesis. It is believed, therefore, that muscle tissue is in possession of certain enzymes which are capable of instigating these processes. Their function is proteolytic, lipolytic and amyolytic. They also act as oxidases or peroxidases, reductases, deaminases, etc. The products of muscular metabolism frequently exert a certain influence upon the function of other structures. Thus, lactic acid and carbon dioxid serve as stimulants to the respiratory center, while the accumulation of these and other bodies in consequence of disturbances in their excretion, may give rise to toxic symptoms.

The Chemical Changes in Contracting Muscle.—The metabolic alterations in the contracting muscle are characterized by a constancy of the catabolism of the proteins and an increase in the catabolism of the carbohydrates, together with a production of lactic acid and carbon dioxid. This is clearly shown by the fact that muscular work does not augment the nitrogen output of the muscle nor of the body, but is

¹ Tetanus, eine physiol. Studie, Leipzig, 1865.

² Grindley and Woods, Jour. Biol. Chem., ii, 1906, 309; Urano, Hofmeister's Beiträge, ix, 1906, 104, and Meyers and Fine, Jour. Biol. Chem., xv, 1913, 283.

³ Gulewitsch and Amiradzibi, Zeitschr. phys. Chem., xxx, 1900, 565.

followed by (a) a greater production of carbon dioxide and a greater consumption of oxygen, (b) a formation of lactic acid, and (c) a gradual disappearance of the glycogen. Hence, as the contraction of a muscle is made possible by chemical alterations in the myoplasm, it must be evident that this energy is chiefly derived from the carbohydrates. The statement that this foodstuff is the most available source of muscular energy, is substantiated further by the fact that muscular exercise immediately raises the respiratory quotient.

The production of carbon dioxide by the active muscles is clearly proved by the fact that the expired air contains a larger amount of carbon dioxide than the inspired. Obviously, this gas is transferred from the tissues to the blood and is subsequently gotten rid of through the respiratory channel. It has also been shown that an excised muscle evolves a much larger quantity of carbon dioxide when tetanized than when allowed to rest.¹ This increased production of carbon dioxide is associated with an increased intake of oxygen, but the respiratory quotient, $\frac{\text{CO}_2}{\text{O}_2}$, increases, because the output of carbon dioxide exceeds the absorption

of oxygen. Moreover, this evolution of carbon dioxide ceases if no oxygen is allowed to enter the body. In explanation of these phenomena it has been stated that this gas does not constitute a primary product, but arises secondarily in consequence of the oxidation of the products of muscular metabolism.² Thus, it has been assumed that the chemical processes in muscle result first of all in a decomposition of the complex nutritive material into intermediary substances, such as lactic acid, which are then reduced in the presence of an adequate supply of oxygen.

This explanation finds substantiation in the fact that frog's muscle, when suspended in an atmosphere of nitrogen, soon ceases to respond to stimulation. If it is then subjected to an analysis, it will be found to contain 0.2 per cent. of lactic acid, but only traces of carbon dioxide. The latter, in all probability, have been liberated in consequence of the change of the muscle medium from faintly alkaline to acid. Conversely, if a muscle is first fatigued in an atmosphere of nitrogen, and is then transferred into a medium of pure oxygen, it soon recovers its irritability and may be stimulated for a long time before it again exhibits indications of fatigue. On subsequent analysis, it will be found to contain practically the same amount of lactic acid as resting muscle, but much larger quantities of carbon dioxide. A contracting muscle, therefore, liberates carbon dioxide in amounts which are almost directly proportional to the quantity of oxygen available for the reduction of the lactic acid.

The Formation of Lactic Acid.—Resting muscle exhibits a neutral or feebly alkaline reaction, while active muscle is distinctly acid.³ This general statement, as we have just seen, holds true only if inconsiderable amounts of oxygen are available, because a copious supply of this gas reduces the sarcolactic acid still further, while a scarcity of it causes the acid to accumulate. But, since mechanical manipulation and thermal and chemical irritations are very prone to increase the production of this acid, it is difficult to obtain an excised muscle with a perfectly neutral reaction.⁴ In most cases it will show an acidity equalling 0.02 per cent., expressed as zinc lactate. This may be considerably increased (0.2 per cent.) by causing the muscle to undergo a few contractions. Blue litmus paper will then be reddened and brown turmeric paper turned yellow.

The production of lactic acid during muscular activity may be proved by injecting a solution of acid fuchsin into the dorsal lymph sac of a frog, whence it will be

¹ Hermann, *Unters. über d. Stoffwechsel d. Muskeln.*, Berlin, 1867.

² Fletcher, *Jour. of Physiol.*, xxviii, 1902, 474.

³ Proved by DuBois-Reymond, in 1859.

⁴ Fletcher and Hopkins, *Jour. of Physiol.*, xxxv, 1907, 247; and xliii, 1911, 12.

absorbed and distributed to the different tissues through the circulation, but as the different media of the body are normally neutral or faintly alkaline, no change in color will result. If one of the posterior extremities is now tetanized by stimulating its sciatic nerve, the muscles so activated gradually assume a reddish hue. This change appears more quickly, if the corresponding femoral artery is ligated after the injection of the fuchsin, because lessening the oxygen supply greatly favors the accumulation of lactic acid.

The origin of the lactic acid in muscle has been the subject of much controversial discussion. Some investigators, indeed, have sought to displace the old view of Liebig which holds that the acidity of muscle is due to the formation of lactic acid, by the theory that it is caused by the mono-phosphate of potassium.¹ Again, it has been assumed that the free lactic acid acts on the potassium biphosphate normally present in muscle and forms potassium lactate by the reduction of the neutral into acid phosphate. It is also believed that lactic acid arises in the course of the disintegration of glycogen, but this view seems untenable because it has been shown that the glycogen content of muscle in death-rigor remains practically the same, in spite of the fact that its content in lactic acid is very high, namely 0.5 per cent. In addition, it has been proved that muscles which have been deprived of their glycogen by fasting, yield as much lactic acid as normal muscles. Hill,² moreover, claims that the precursor of lactic acid is a substance which possesses a heat value at least 70 per cent. greater than that of this acid. But the heat liberated by dextrose, is only slightly greater (3 per cent.) than that of lactic acid, and furthermore, an excised muscle frequently yields a quantity of acid which is considerably above that actually to be derived from the glycogen normally present in muscle. These results clearly demonstrate that glycogen cannot be the mother-substance of this acid. The only alternative, therefore, is that it is a derivative of the proteins. More recently, it has been asserted that muscle tissue contains a carbohydrate-phosphoric acid group which yields lactic and phosphoric acids in about equimolecular amounts. It is believed that the sugar of muscle is synthesized with phosphoric acid and other constituents into the aforesaid complex compound. On breaking down, the carbohydrate group of this body gives rise to lactic acid.

The Disappearance of Glycogen.—Weiss³ has shown that frog's muscle loses from 24 to 50 per cent. of its glycogen on tetanization. This observation has been confirmed repeatedly by other investigators so that it may now be considered as definitely proven that this constituent of muscle diminishes during activity. A normal resting muscle, on the other hand, increases its store in glycogen and much more rapidly, if its motor nerve is cut to prevent contraction. In a similar way, it may be proved that general muscular exercise reduces not only the glycogen store of the muscles, but also that of the liver. This consumption of glycogen may be rendered even more striking by temporarily discontinuing the intake of food. Cardiac muscle, in particular, possesses very marked storing qualities, and retains its glycogen even more tenaciously than skeletal muscle.⁴

The liberation of heat and electrical changes concomitant with muscular contraction, will be discussed in a later chapter. Suffice it to say at this time that the muscles constitute the chief heat producing tissue of our body and that their activity is associated with clearly recognizable electrical variations.

The Chemistry of the Fatigue of Muscle.—We have previously seen that the continued or excessive stimulation of muscle eventually causes it to become functionally useless. It loses its irritability and contractility so that even the strongest stimulus is no longer able to

¹ Dreser, *Zentralbl. für Physiol.*, i, 1887, 195.

² *Jour. of Physiol.*, xlv, 1913, 28.

³ *Sitzungsb. der Wiener Akad.*, lxiv, 1871.

⁴ Aldehoff, *Zeitschr. für Biol.*, xxv, 1889, 137.

activate it, and naturally, an excised muscle is more susceptible to fatigue than a normal one, because it is quite unable to obtain new material and to discharge the products of its metabolism. Likewise, it may be inferred that a normal muscle is able to regain its functional qualities within a relatively short time, while an excised muscle is not.

This exhaustion, therefore, is referable to two causes, namely an insufficient supply of nutrient material, inclusive of oxygen, and an accumulation of depressing waste products. The fact that substances of this kind are actually formed, needs no further substantiation, because Ranke¹ has shown that the irritability of a fatigued muscle may be restored by perfusing it with an ordinary non-nutritive solution, such as sodium chlorid. In addition, this investigator has proved that the injection of extracts of the fatigued muscles of one frog into the circulation of another gives rise to a typical depression in the second animal. Inasmuch as these results can also be obtained with solutions of lactic acid and creatin, he gave to these agents the name of "fatigue substances," and later on included under this term also carbon dioxid and acid potassium phosphate. (KH_2PO_4). More recently Mosso² has extended these experiments to warm-blooded animals and has shown that the transfusion of the blood of a fatigued dog into the circulatory channels of a second perfectly normal dog produces in the latter most decided symptoms of fatigue.

Weichardt³ has attempted to add to the three fatigue substances carbon dioxid, lactic acid and monopotassium phosphate, also a certain specific muscle toxin which he calls kenotoxin. When isolated from the other substances, this toxin, when injected into other animals, is capable of producing the phenomena of fatigue. He also claims to have obtained, by bacteriological methods, an antitoxin which serves to counteract the effects of this toxin and to retain the muscle in a reactive condition. These tests have more recently been repeated by Lee and Aranowich,⁴ but no evidence has been found to substantiate the formation of an actual muscle toxin.

It has also been shown by Lee⁵ that small quantities of any of the three fatigue substances previously mentioned, cause a temporary augmentation in the activity of the muscle, as is evinced by an increase in its irritability and working power. Thus, if a muscle is successively stimulated at intervals of, say, one second and its contractions are registered upon a slowly revolving drum, the injection of a small amount of any one of these agents temporarily increases the height of these contractions. In this manner the curve may be made to show periodic augmentations. This phenomenon is known as the "Treppe." In this connection it might also be mentioned that these staircase-

¹ Tetanus, Leipzig, 1865.

² Arch. de biol. ital., xiii, 1890.

³ Münchener med. Wochenschr., li, 1904, 12; lii, 1905, 1234; and liii, 1906, 1701.

⁴ Proc. Exp. Soc. of Biology and Medicine, 1917.

⁵ Am. Jour. of Physiol., xx, 1908, 170.

like increases are frequently observed at the beginning of a series of contractions of either striated, non-striated or cardiac muscle when stimulated with induction shocks of constant strength. According to Lee, this initial "Treppe" is due to a sudden increase in the irritability of the muscle, following the early production and accumulation of small quantities of the fatigue substances. It may be accepted as proven that the seat of this excitation is the myoplasm and not the neuroplasm, because these increases also develop in curarized muscles and in muscles which have suffered a degeneration of their nervous elements.

The Chemistry of Rigor Mortis.—The condition of death rigor is characterized by a rigidity of the musculature which makes its appearance very shortly after the general functions of the body have ceased. It manifests itself by a loss of the irritability and contractility of the myoplasm. The muscle becomes opaque, stiff, and firm to the touch and, unless its tendency to shorten is opposed by a slight counterforce, is prone to assume a state of very slight contraction.

Under ordinary conditions, rigor mortis affects the different muscles in a definite sequence from above downward, beginning with those of the jaws and neck and finally involving those of the trunk, arms and legs. It is also noted that these muscles are affected gradually, *i.e.*, fiber after fiber and not simultaneously throughout their substance. The degree of their shortening is determined by the weight of the part moved by them and the force opposing this tendency. Thus, the simultaneous stiffening of the flexors and extensors finally gives rise to a fixed position of the extremities so that the joints become immovable, but inasmuch as these muscles are antagonistically placed, practically no shortening results. This fact that the muscle in rigor retains its normal form almost completely, may be more plastically portrayed by cutting the tendons of either the flexors or extensors of the foot at death. It will then be found that the subsequent rigor of the opposing muscles does not materially change the position of the foot.

The time required for the development of rigor mortis is very variable. Most generally it makes its appearance in from 1 to 5 hours, but in some cases it may begin as early as 10 minutes after death. A delay of from 20 to 24 hours is not unusual. Under certain conditions it may develop almost instantaneously, giving rise to the so-called cataleptic rigor. Thus, it is narrated that soldiers have been found in rigor with the gun at their shoulders and with one eye open and the other closed as in the act of taking aim. In all these and similar cases, the central nervous system was found to have been seriously lacerated. The duration of rigor mortis is also very uncertain, because it may last anywhere from a few hours to a few days, or even a week. A quick onset, however, usually suggests a short duration. Forced movement of the parts frequently tends to bring on relaxation.

The factors which may be held responsible for this variation in the

character of rigor mortis are several. First of all we might mention the condition of the muscles at the time of death. Thus, it is a matter of common observation that muscles which have been enfeebled by disease show a rapid onset and dissolution, while strong and vigorous muscles are affected rather slowly. Cold delays and warmth hastens its onset. The same is true of muscular fatigue and certain diseases of the spinal cord and brain. Extensive lesions of these parts greatly favor its development. Young individuals, and especially infants, are affected more rapidly than adults, and red muscles more slowly than pale muscles.

In analogy with muscular contraction it is believed that rigor mortis is caused by a coagulation of the protein material. It is held that the myosin and myogen are temporarily converted into their insoluble forms,¹ myosinfibrin and myogenfibrin, this change being associated with an increase in the acidity of the muscle. Inasmuch as the latter is dependent upon the production of lactic acid, it has been assumed that this acid is the actual cause of this coagulation, or is at least very closely concerned with it. This inference is entirely justified, because lactic acid is not copiously produced in the presence of an abundant supply of oxygen. Rigor mortis then fails to develop. A deficiency in oxygen, on the other hand, favors the accumulation of lactic acid and hence, also the occurrence of this condition. In accordance with this conception, the dissolution is said to be dependent upon the reestablishment of the neutral reaction of the medium or upon intracellular autolyses due to ferments.² It has been proved, however, that bacteria are not the primary cause of the dissolution, because the rigor also disappears when their growth is prevented.³ In analogy with the coagulation of the blood, the attempt has also been made by Danilewsky⁴ and others to bring the development of rigor mortis into relation with the calcium content of the muscle plasma. We have previously seen that this relationship is only a general one; moreover, it has been shown that calcium-free solutions of myogen are not exempt from coagulation.⁵

In the third place, a muscle in rigor mortis gives rise to a considerable amount of carbon dioxid which may have its source either in an increased general catabolism or in those oxidations which are primarily concerned with the reduction of lactic acid. In accordance with the experiments of Fletcher and Brown,⁶ this point has been decided in favor of the latter view, the increase in carbon dioxid being the indirect result of the formation and oxidation of the lactic acid. Some observers also claim that the glycogen content of muscle is diminished during rigor mortis.

¹ Saxl, Hofmeister's Beiträge, ix, 1906, 1.

² Vogel, Deutsch. Arch. für klin. Med., 1902, 292.

³ Bierfreund, Pflüger's Archiv, xliii, 1888, 195; and Karpa, *ibid.*, cxii, 1906, 199.

⁴ Zeitschr. phys. Chemie, vi, 1882, 158.

⁵ v. Fürth, Hofmeister's Beiträge, iii, 1903, 453.

⁶ Jour. of Physiol., xlviii, 1914, 177.

The Chemistry of Rigor Caloris.—It has previously been shown that the continued application of heat causes the muscle to lose its irritability and to become functionally useless. In this condition of rigor caloris the muscle presents an opaque appearance, a firm consistency and a change in its form, approaching its state of maximal shortening. The skeletal muscles of the frog enter this condition at 40° or 41° C., while those of warm-blooded animals require a temperature of about 47° C. This difference in their behavior may be ascribed to the fact that the muscles of amphibia contain preformed soluble myogen fibrin which coagulates at 40° C., while those of mammals contain soluble myosin which coagulates at 47° to 50° C. While rigor caloris may be said to be dependent upon a conversion of the proteins¹ into their insoluble forms, a muscle entering this condition also liberates carbon dioxid and heat, and acquires a larger store of lactic acid. Fletcher claims that this carbon dioxid is preëxisting and is set free at 40° C. from carbonates and similar bodies through the intervention of the lactic acid. At higher temperatures (75° C.) it is given off by the colloids and amino-acids.

Muscles may also be thrown into a state of rigor by means of a number of chemical substances. Water-rigor, for example, results in consequence of their immersion in distilled water, while coagulation-rigor is the outcome of the coagulation of their protein material by such agents as alcohol and chloroform.² The same result may be obtained with dilute acids, veratrin, caffein, quinine and different toxins.³ While it is often difficult to differentiate between these different types of rigor, heat rigor may easily be distinguished from death rigor, because the former is a permanent and the latter a temporary condition. Furthermore, a muscle in rigor caloris shows a more decided opacity, and possesses a more solid consistency than a muscle in rigor mortis. The latter is rather unevenly turbid and its color may be considerably lightened by a 0.2 per cent. solution of sulphuric acid.

CHAPTER X

THE PRODUCTION OF ENERGY IN MUSCLE

Forms of Energy Liberated.—Life manifests itself by incessant changes and every manifestation of it necessitates the liberation of energy in some form or other. Work must be done and a body that cannot yield energy, accomplishes neither changes nor work. But since the law of the conservation of energy applies equally to all living entities, these alterations cannot be associated with a gain or loss in

¹ v. Fürth, *loc. cit.*; Inagaki, *Zeitschr. für Biol.*, xlviii, 1907, 313, and Meiggs, *Am. Jour. of Physiol.*, xxiv, 1909, 178.

² Brooks, *Am. Jour. of Physiol.*, xvii, 1906, 218.

³ Heinz, *Handb. der exp. Path. und Pharm.*, i, 1905, 576.

material. It merely means that one kind of energy is transformed into another without actually causing a change in the total amount of the energy available in the universe. It is true, however, that the proportion of "bound" and "free" energy does not remain the same; in fact, the latter invariably diminishes and never increases. Like all protoplasm, muscle tissue contains a store of chemical substances from which it derives its necessary energy. When stimulated, certain chemical processes of an explosive type are initiated in its substance which cause its potential energy to be converted into kinetic energy. The latter presents itself as mechanical work, heat and electricity, light being excluded in this particular case. But naturally, the relative amounts of these three forms of energy must vary considerably, the production of heat greatly exceeding that of mechanical energy and electricity. Individual variations are common and find their origin in the character of the muscle tissue as well as in the conditions under which it is made to contract. Thus we find that the muscles of warm-blooded animals are able to do twice as much work per unit of mass as those of cold-blooded animals and that the muscles of insects are even more powerful than these. It has already been mentioned that red striated muscles are more powerful than pale muscles, the greater effectiveness of the latter lying rather in their quickness of action than in their actual strength. The liberation of energy is affected unfavorably by fatigue, low temperatures, a high humidity of the air, a poor nutritive condition of the body, and other factors. In general, however, it may be said that about one-third of the total amount of energy appears in the form of mechanical energy and somewhat less than two-thirds in the form of heat.¹ Fick,² working with excised muscles, states that under favorable conditions about one-fourth of the total energy can be given off as mechanical work, provided the load used is relatively large. With smaller weights this amount is proportionately diminished.

The Work Performed by Muscle.—For ordinary purposes it suffices to determine the work performed by a muscle by simply multiplying the load by the height to which it has been lifted. The product is then expressed in terms of milligram-meters. Thus, if a muscle raises a weight of 25 grams to a height of 10 millimeters, as determined by the weight of the curve recorded by it upon the kymograph, it has done 250 gram-millimeters of work. In this calculation, however, an allowance must be made for the magnification of the writing lever in accordance with the formula: $L:H :: l:h$, in which L equals the total length of the lever, l the length of its short arm from the axis to the attachment of the muscle, H the height of each line of contraction and h the actual height to which the load has been lifted. The work (W) is then computed in gram-millimeters in accordance with

¹ Zuntz, Pflüger's Archiv, lxxviii, 1897, 191.

² Ibid., xvi, 1878, 85.

the formula: $W = wh$, in which w signifies the weight and h the height to which it has been raised.

From these results it may be gathered first of all that the product must become zero if no weight at all is attached to the muscle. When not loaded, therefore, a muscle does practically no external work and the chemical changes occurring during its contraction are almost wholly converted into heat and a small amount of electricity. The word "practically" is inserted here, because a muscle even when not carrying a weight, must overcome its own resistance which, to be sure, is so slight that nearly all of its energy can appear as heat. This modification could of course be rendered superfluous by adjusting the muscle in a horizontal manner and immersing it in oil to overcome this friction as much as possible. In the second place, it is also evident that the product must become zero if H equals zero, and even when the muscle is loaded with so heavy a weight that it is quite unable to lift it. As in the preceding case, most of the energy liberated is then turned into heat.

Attention should also be called to the fact that a muscle which merely contracts and relaxes, raising and lowering a weight, really furnishes no energy to its surroundings, because it develops no kinetic energy at this time. In order to accomplish actual work, it would be necessary for it to produce certain changes. This end it could easily accomplish by raising a weight to a definite height and permitting it to fall to the surface of the earth. The potential energy stored in it would then be converted into kinetic energy.

We have previously seen that a muscle, when properly counterpoised and made to react successively against a steadily increasing load, exhibits a gradual decrease in the height of its contractions. Eventually a weight will be found which it is quite unable to lift. At this time, therefore, the load counteracts the contractile power of the muscle and no mechanical energy is liberated. This weight which merely places the muscle under a maximal degree of tension and does not permit it to change its length, has been designated by Weber as the *absolute power of the muscle*. Moreover, since this power is proportional to the cross-section of the muscle, we are in a position to obtain a standard by simply determining the absolute force for one square centimeter of muscle substance. This value, to be sure, differs in different muscles, because such factors as the character of the myoplasm and the number and arrangement of the muscle fibers, give rise to individual variations. For frog's muscle, values ranging between 0.7 and 3.0 kilograms per centimeter of cross-section have been found. The experiments upon human muscles have been made during voluntary contractions and not during artificial tetanization, while the cross-sections of the muscles employed for these tests have been determined upon dead subjects of the same physique as the person experimented upon. Hermann¹ gives the average absolute force of human muscle

¹ Pfüger's Archiv, lxxiii, 1898, 429.

as 6.25 kilograms, a value which is considerably higher than the preceding one for frog's muscle. This calculation becomes of practical value in testing the power of the muscles of persons suffering from various types of nervous diseases. A so-called dynamograph is commonly used for these determinations. This instrument consists of a tension-spring against which the muscles of the hand are voluntarily contracted.

A close study of the curve represented by Fig. 43 also shows that a muscle reacts better when a slight load is attached to it than when it is not weighted at all. To begin with, therefore, the contractions increase in height, quickly at first and then more slowly, until a certain

FIG. 52.—DIAGRAM OF WORK-ADDER.

A, wheel which is turned by muscle *M* in direction of arrows. It is held in place by brake *B*. Each contraction of muscle raises weight *W*.

maximum has been reached. Subsequent to this point the increasing loads gradually diminish the contractions until the muscle is no longer able to raise the lever above the abscissa. Hence, a muscle yields maximal work only when made to act against a certain moderate weight which places it under a physiological tension.

In order to determine the work performed by a muscle during a long period of time, it becomes necessary at times to employ an ergograph or a work-adder.¹ The former instrument has been described in an earlier chapter. The latter consists of a small windlass which the muscle (*M*) turns slightly in one direction with each contraction. The weight (*W*) which is suspended from the wheel (*A*) by a thread is

¹ Fick, *Unters. aus dem physiol. Lab. der Züricher Hochschule*, Wien, 1869.

raised a certain distance with every contraction, its descent being guarded against by an automatic brake (*B*) which retains the wheel in its newly acquired position during the subsequent resting period of the muscle. At the end of this experiment the total work performed by the muscle, may be computed by multiplying the weight by the height to which it has been raised.

The Muscle as a Thermogenic Organ.—We have seen that the largest amount of the energy liberated by the body leaves it in the form of heat. We are also justified in concluding that this heat is derived very largely from the activity of the musculature, because the latter constitutes about 40 per cent. of the total weight of the body and, after the removal of the skeleton, more than 50 per cent. The bones, as may readily be surmised, do not possess a vivid metabolism, while that of the muscles is greater than that of any other tissue. Thus, it is a matter of common experience that the temperature of the body increases very markedly during exercise, frequently to 39° or 40° C.,

FIG. 53.—ARRANGEMENT OF THERMOELECTRIC ELEMENTS (*A* and *B*) AND GALVANOMETER *C*.

but this rise is only temporary in its nature, because the heat is again dissipated during the subsequent period of relative muscular rest. The production of heat may also be registered locally in the contracting muscles of the thigh or arm of a mammal, the bulb of a thermometer being pushed in among the muscle fibers (Gierse, 1842). More exact values, however, may be obtained with the help of thermoelectric elements, but naturally, the *thermoelectric method* necessitates a much greater experimental aptitude than the *thermometric*.

A thermoelectric couple consists of two dissimilar metals, such as German silver and iron or antimony and bismuth (*A* and *B*). These are soldered together and the binding post upon each couple connected with a low resistance galvanometer (*C*). In investigating the heat production of muscle, one of these couples is inserted with its pointed tip in an indifferent muscle, while the other is placed in the muscle to be experimented upon. As long as this muscle remains inactive, it generates no heat, and hence, no electric differences are developed at the points of soldering. The needle of the galvanometer remains stationary. If the muscle is now made to contract, this system immediately ceases to be isoelectric, because the heat produced therein generates an electric difference in the corresponding thermopile which in turn leads to a definite deflection of the galvanometric needle.

By equipping this indicator with a small mirror, a beam of light may be reflected from it upon a screen or into a photographic camera. Its excursions are standardized with the help of a very sensitive thermometer.

Becquerel and Bichet (1835) who first employed this method upon the biceps muscle of a human subject, obtained a rise of 0.5°C . during energetic movements. In a similar way, Helmholtz (1847) has found that the tetanization of a frog's muscle raises its temperature $0.14\text{--}0.18^{\circ}\text{C}$., while Heidenhain¹ has noted a rise of 0.005°C . during single contractions. It must be remembered, however, that even a resting muscle serves as a thermogenic organ, because the blood returned from it possesses a higher temperature than that passing into it (Ludwig, 1881). In addition, it has been ascertained that the heat production varies directly with the intensity of the chemical changes. A strong stimulus, therefore, must yield more heat than a weak one. Tension has a similar influence, because isometric contractions are followed by a greater liberation of heat than isotonic. Weight acts favorably at first, on account of its initial tendency to augment the mechanical energy; later on, however, the liberation of heat diminishes more rapidly than the amount of work. These and other facts tend to show that a muscle works more economically when acting against a moderate load than when not weighted at all. Furthermore, when a fresh muscle and a fatigued muscle are made to perform the same amount of work, the former generates more heat than the latter, because it is in possession of a greater store of chemical substances.

The Muscle as an Electrogenic Organ.—The electrical current generated by a battery finds its origin in chemical changes enacted by its constituents. In quite the same way, the differences in electrical potential developed by muscle and other forms of protoplasm, find their cause in chemical alterations accompanying their activity, and hence, are derived from their stored potential energy. The amount of electrical energy developed by muscle is rather small, but it should not be forgotten that this amount is considerably augmented by the sum total of the electricity which is evolved by the glands, nervous structures and other tissues. The final result, therefore, is far from trivial.

It need scarcely be mentioned that certain animals, for example, the electric fish, possess special organs for the generation of this form of energy to serve as a weapon of offense and defense. It is stated that *Malapterurus electricus* inhabiting the rivers of Africa (Nile), is capable of producing a shock equalling 200 volts. The organ itself is situated directly below the skin on each side of the body and consists of a number of membranous plates arranged parallel to one another. In *Gymnotus* and *Malapterurus* these plates are placed vertically and in the *Torpedo* horizontal to the long axis of the body. Each organ is innervated by a nerve which subdivides and sends branches to each plate. In *Malapterurus* this nerve is but a single giant fiber possessing a very thick investment and derived from a single large ganglion cell. The long discussions, whether these electrical organs consist of modified muscle or nerve tissue or whether they are embryologically distinct, have led to the conclusion that those of *Torpedo* and *Gymnotus* have been derived from muscle tissue, while that of *Malapterurus* is an outgrowth of the skin glands.

Schönlein has estimated the electromotive force of an entire organ of the *Torpedo* at 0.08 volt for each plate; hence, it equals that of thirty-one Daniell cells. This voltage is sufficient to kill other fish and animals and especially because it is discharged in transverse lines. The discharge results chiefly in a reflex manner upon mechanical stimulation. In *Malapterurus* the shock traverses the conductor in a direction from the head to the tail of the animal and in *Gymnotus* from the

¹ Mechanische Leistung, etc., Leipzig, 1864; also see: Fick, Myotherm. Untersuchungen, etc., Wiesbaden, 1889.

tail to the head. Peculiarly enough, the fish itself is fully protected against these shocks, a fact which is generally referred to the extremely low degree of irritability of its tissues.

Animal electricity, or as it is known in Physics, *galvanism* was discovered by Alvisio Galvani in 1786. In the course of his experiments upon the influence of atmospheric electrical discharges upon animal life, he attached the leg of a frog to a copper hook and placed this preparation upon the iron railing of the veranda of his house. When he did so, the muscles twitched violently. He explained this phenomenon by saying that the muscles themselves generate electricity. Volta, however, gave a very different and, as it finally proved, more correct explanation of this reaction. He assumed that whenever two dissimilar metals are connected with a moist conductor, a difference in electrical potential is established which is equalized as soon as these metals are joined. Peculiarly enough, Galvani not only adhered to his former contention, but endeavored to find further substantiation for it. He placed a muscle preparation upon a glass plate and brought the end of a freshly cut nerve in contact with its surface. Whenever contact was made between them, the muscle twitched violently. He thus became the discoverer of animal electricity after having just convincingly recognized contact electricity.

Methods of Detecting Electrical Variations in Muscle.—The existence of electrical currents in the tissues of animals and plants did not find direct proof until the year 1824, when Schweigger discovered the multiplier and Nobili the galvanometer. A few years later, Nobili also proved that "natural currents" occur in the frog, which pass in a direction from the foot toward the head of the animal.

The ordinary form of *galvanometer* consists of a ring magnet which is suspended by means of a silk fiber and rests in relation with a number of vertical coils, each of which is composed of many windings of fine copper wire. If an electric current is passed through this system of wires, the neighboring magnetic field is influenced in such a way that the magnet is deviated from the magnetic meridian either to the left or right in accordance with the direction of this current. These deviations are registered as a rule by equipping the pointer or needle of the magnet with a small mirror, from the surface of which a beam of light may be reflected upon a screen or upon sensitive paper contained in a photographic camera (Thompson). In order to protect the galvanometer against the magnetism of the earth, two magnets of nearly the same strength are placed in opposite directions near the instrument. As the magnets tend to point toward the poles, they oppose one another and thus compensate in part for the earth's magnetism. The Deprez d'Arsonval galvanometer embraces certain modifications which, in addition to those just mentioned, diminish the disturbances otherwise prone to result from currents made to traverse neighboring circuits for purposes of light and electric power. The principal element of this instrument is a wire which is hung between the poles of an electromagnet. Inasmuch as this wire is bent upon itself to form a spiral, it is not deflected laterally but is merely twisted in a rotatory manner. Its movements are registered by a mirror from which light is reflected.

An instrument of similar construction but capable of a much greater rapidity of motion, is the *string galvanometer*, devised by Einthoven.¹ It consists of a power-

¹ Arch. intern. de Physiol., iv, 1906, 133, and Pflüger's Archiv, lxxii, 1908, 517.

ful electromagnet possessing the shape of a horseshoe. A delicate thread of silvered quartz or platinum is suspended in a vertical direction between its two

FIG. 54.—D'ARSONVAL GALVANOMETER AS MODIFIED BY ROWLAND WITH TELESCOPE FOR OBSERVING MOVEMENTS OF NEEDLE. (Howell.)

FIG. 55.—SCHEMA OF GALVANOMETER.

n, s, North and south poles of astatic pair of magnets; *m*, compensating magnet, held by friction on the staff, and capable of being approached to, or rotated with reference to, the suspended magnet; *x*, mirror; *f*, fiber supporting the magnets; *c, c, c, c*, coils of wire to carry the electric current near to the magnets, the upper coils being wound in the opposite direction to the lower; *e, e*, non-polarizable electrodes applied to the longitudinal surface and cross-section of a muscle. (*American Text-book of Physiology.*)

poles. The sides of these poles are perforated so that the shadow of this string may be reflected upon a screen or upon the sensitive paper of a photographic camera.

If an electric current is permitted to pass through it, it is moved laterally in a line parallel to the poles, *i.e.*, perpendicularly to the lines of force passing between the poles of the magnet. These deflections take place to either side in accordance with the direction of the current. Contrary to the d'Arsonval galvanometer, the deflections of this string are not mere twists but actual lateral deviations which can be increased and decreased by varying the tension placed upon the string. Knowing this tension, or, in other words, the resistance of the string, the strength of the current causing its deviations, may be calculated directly from the size of the deflections. The string galvanometer permits of a freedom of motion which the ordinary forms of galvanometer cannot attain, although the actual sensitiveness of the latter is no doubt greater than that of the former. Thus, its chief character-

FIG. 56.—EINTHOVEN'S STRING GALVANOMETER, AS MODIFIED BY CUNNINGHAM, WILLIAMS AND HINDLE.

The front-cover has been removed to show the position of the string between the poles of the magnet. The connecting posts lie behind the hood containing the string.

istic is its speed of reaction which enables it to follow the electrical variations with an almost immeasurable exactness.

A third instrument which is sometimes used for the detection of electrical currents of animal origin, is the *capillary electrometer* (Lippmann, 1877). A glass tube is drawn out at one end into a tube of capillary size and is filled with mercury up to and beyond the point of entrance of a copper wire (A). This tube is then placed vertical and is made to dip into a cup-shaped receptacle which is filled with mercury and is pierced by a copper wire (B). A small quantity of dilute sulphuric acid is now placed over the mercury in the cup. If the capillary is of proper size, the mercury does not flow out, but is held at a definite level. By compressing a small rubber bulb which is connected with the upper end of this tube (P), the mercury is then forced downward and upward a number of times until the lower lumen of the capillary tube is completely filled with the acid. The level of the mercury or meniscus (M) is adjusted under the objective of a microscope (L); in fact, it may be projected upon a screen or upon sensitive paper. If an electrical current is now

passed through these conductors by way of the two copper wires, the surface tension of the mercury is changed, forcing the meniscus to move either upward or downward in accordance with the direction of the current. If its point of entrance (anode) is below, the meniscus moves upward, and vice versa.

FIG. 57.—CAPILLARY ELECTROMETER.

A, tube and B, receptacle filled with mercury; M, meniscus of mercury; L, lens of microscope; P, tube leading to small rubber bulb for adjusting meniscus.

of a post which may be pushed back and forth upon the wire. By moving this sliding post (D) nearer to or farther away from the end post (B), a greater or less amount of the current generated by the battery is allowed to oppose the

The strength of this electrical current may be determined by noting the extent of the movement of the meniscus, because a direct relationship exists between these two factors. It may also be measured by interposing a resistance in the circuit outside the electrometer or galvanometer which is just sufficiently powerful to force the meniscus or the galvanometric needle to assume its normal position. At this very moment the resistance neutralizes the current, and hence, the number of ohms necessary to accomplish this end must correspond precisely to the difference in the electrical potential. Most generally, however, we make use of the so-called *compensation method* which requires the use of an artificial current in a direction opposite to that produced by the muscle. This end may be attained most easily with the help of a rheocord (Fig. 58), consisting of a certain length of German silver wire. The two binding posts at the ends of this wire (A and B) are brought into connection with the poles of a battery cell. The circuit of the electrometer or galvanometer (C) with its muscle preparation (M) is then brought into relation with the resistance wire by a lead from one of its posts, while the return lead is effected by means

FIG. 58.—THE SIMPLE RHEOCORD.

AB, German silver wire; C, galvanometer; M, muscle; D, sliding post; K, key.

muscle current until an equalization has finally been attained. Knowing the strength of the counter current, the strength of the muscle current may be determined from the resistance which has been interposed, *i.e.*, from the position occupied by the sliding post. The value of the action current of an ordinary muscle scarcely exceeds 75 millivolts; its usual strength is 0.06–0.08 volt.¹

¹ Samjloff, Pflüger's Archiv, lxxviii, 1899, 1.

The Character of the Electrical Variations in Muscle. Current of Injury and Current of Action.—If a perfectly normal resting muscle is connected with two non-polarizable electrodes which in turn communicate with a galvanometer, the indicator of this instrument remains perfectly stationary. The reason for this is that an uninjured and inactive muscle is isoelectric, *i.e.*, it does not present differences in electrical potential which could give rise to a current (Hermann). This condition, however, does not prevail if a muscle is isolated in the usual way and is then removed from the body, because it is scarcely possible to do this without injuring it. On being connected with a galvanometer, such a muscle immediately deflects the needle, because it is no longer isoelectric. A current is set up in consequence of these differences which, in accordance with the direction of the deflection of the galvanometric indicator, passes from the uninjured to the in-

FIG. 58a.—THE CURRENT OF INJURY.

M, muscle; *G*, galvanometer; *J*, seat of injury.

jured portion of the muscle (Fig. 58). Viewed from the outside, therefore, the uninjured portion of a muscle is positive (anode) and the injured portion negative (cathode). But inside the muscle, the current passes from the injured portion to the uninjured, so that the former constitutes its positive and the latter its negative pole. Most commonly, however, we characterize this current as galvanometrically negative, because notice is taken only of its direction outside the muscle.¹ This current is usually referred to to-day as the *current of injury*, although Hermann has called it the demarcation current, and Matteucci,² the current of rest. The latter designation has its origin in the fact that the resting muscles of the thigh of the frog yield an electrical current whenever they are cut across transversely and connected with a galvanometer. A few years later, however, Du-Bois-Reymond³ proved that resting muscles are isoelectric and that the current of rest is really a current of injury.

¹ Biedermann, *Ergebn. der Physiol.*, ii, 1903, 173.

² *Transact. Acad. des sciences de Paris*, 1838-42.

³ *Unters. über tier. Elektrizität*, Berlin, 1848.

This electrical difference persists as long as the injury. The same conditions prevail in a degenerating muscle, its degenerated portion being galvanometrically negative to its normal portion, but naturally, these differences cease as soon as the degeneration has progressed evenly throughout its substance. Dead tissue gives no current. In order to obtain the current of injury in an unmistakable manner, it is best to employ a cylindrical muscle and to injure it by cutting transversely across one of its ends. One non-polarizable electrode is then placed against this cross-section, while the other is adjusted externally upon the equator of the muscle. In explanation of this current DuBois-Reymond has proposed the so-called molecular theory which assumes that the muscle is built up of a series of the smallest possible molecules which are electrically charged and are surrounded by an indifferent conducting fluid. These individual molecular elements are peripolar, *i.e.*, their equatorial zones are positive and their polar zones negative. The former are directed toward the surface and the latter toward the cross-section of the muscle. Hermann's¹ explanation is based upon the so-called "alteration theory" which assumes that muscle tissue develops no electrical current as long as its chemical constitution remains the same throughout its substance. Electrical differences, however, arise immediately if the chemical equilibrium of any of its zones is disturbed either by injury, degeneration or activity. Oker-Blum² claims that these differences in the electrical potential of a muscle are dependent upon its varying concentration and are caused, therefore, by the speed of movement of its different ionic constituents. Bernstein³ refers them to a process of dissociation. But these theories, as well as the one advocated more recently by Overton⁴ are altogether too incomplete and indefinite to be made the subject matter of a profitable discussion for students.

In 1842 Matteucci made the observation that if the sciatic nerve of one leg is placed upon the muscles of the opposite leg, the muscles of both legs may be made to contract by simply stimulating the sciatic nerve on the normal side. This experiment, which is known as the "induced contraction" or "secondary tetanus," may also be performed in the following manner (Fig. 59). Two muscle-nerve preparations (*A* and *B*) are placed near one another upon a glass plate in such a way that the sciatic nerve of muscle *B* rests lengthwise upon the body of muscle *A*. If the nerve of muscle *A* is now stimulated with a weak induction shock, the reaction involves not only muscle *A* but also muscle *B*. The essential point to be remembered about this experiment which is usually designated as the rheoscopic frog preparation, is that muscle *B* is not stimulated directly by the current applied to nerve *A*, but indirectly by the "*current of action*" generated in muscle *A* in consequence of its contraction.

¹ Handb. der Physiol., Leipzig, i, 1879, 235.

² Pflüger's Archiv, lxxxiv, 1901, 191.

³ Ibid., xcii, 1902, 521.

⁴ Sitzungsab. der ph.-med. Gesellsch., Würzburg, 1905.

In explanation of this phenomenon, it should be stated first of all that the active portion of a muscle possesses a different electrical potential from the resting portion. Thus, if a perfectly normal muscle is brought into the circuit of a galvanometer by means of non-polarizable electrodes, the excitation of one of its ends immediately produces a deflection of the needle (Fig. 60). If the direction of this deviation is now noted, it will be seen that the current flows through the galvanometric circuit from the unexcited to the excited portion of the muscle. Its resting part, therefore, is electropositive to its contracting part. Inside the muscle, of course, the current flows from the contracting to the resting portion, the former being positive and the latter negative. But, as has been stated above, we usually designate the direction of these currents in accordance with their flow through the galvanometer.

FIG. 59.—THE RHEOSCOPIC FROG PREPARATION.

Muscle *A* stimulated through its nerve at *S*, generates an action current which causes muscle *B* to contract.

FIG. 60.—CURRENT OF ACTION.

M, muscle; *G*, galvanometer; *S*, seat of stimulation.

In accordance with these results, it must now be evident that the preceding experiment with the rheoscopic frog preparation, actually proves the occurrence of an electrical variation in muscle in consequence of its activity. Muscle *B* serves in this case the purpose of a galvanometer, because its contraction indicates that such a current is actually present. It may be concluded, therefore, that the excitation of nerve *A* gives rise to a contraction of muscle *A*, in the course of which an action current is set up in its substance which serves as a stimulus for nerve *B*. The impulse generated in the latter produces a contraction of muscle *B*. The function of muscle *A* with regard to muscle *B* may therefore be likened to that of a battery. In order to avoid the possible criticism that the activation of muscle *B* is caused by an escape of the current used to stimulate, it is advisable to subject nerve *A* to mechanical impacts, or to modify the entire experiment by placing nerve *B* lengthwise upon the beating heart of a mammal.¹

¹ Köllicker, Müller's Archiv, vi, 1856, 528.

In the latter case the muscle twitches with every systole of this organ, thereby proving that a current of action is also generated in cardiac muscle.¹ Similar currents arise in glandular tissue during active secretion and in nerves when made to conduct impulses. This phenomenon also manifests itself in the optic nerve when the retina is stimulated by light.

The Different Phases of the Currents in Muscle.—If an injured muscle is brought into the circuit of a galvanometer, the needle of this instrument is deflected almost immediately to indicate a negativity in the region of the injury. The indicator remains in this position as long as the injury lasts. The current of injury, therefore, possesses only one period; in other words, it is monophasic in its nature. The

FIG. 61.—DIAGRAM SHOWING DIPHASIC CHARACTER OF ACTION CURRENT. PHASE I AND PHASE II.

A, active portion; R, resting portion; S, seat of stimulation; G, galvanometer. The current of action is indicated in each case by the arrows.

current of action, on the other hand, is diphasic, or rather polyphasic, because the muscle contracts not only in the region stimulated but successively throughout its substance (Fig. 61). Inasmuch as this contraction does not involve its different segments simultaneously, but consecutively in the form of a wave, the electrical variations must display a similar wave-like character. To begin with, the zone nearest the seat of the stimulation is electronegative to the resting zone (Phase I.) A moment thereafter, however, the wave of contraction has reached the opposite end of the muscle (Phase II), whereas the area stimulated first has become inactive. The negativity then becomes centralized in the region far away from the seat of the stimulation. In order to follow this progressive wave accurately, the galvanometer must first execute a deflection in a direction indicating the negativity of the muscle at the point of stimulation and immedi-

¹ The action current of the heart of mammals has also been demonstrated by A. D. Waller with the help of the capillary electrometer, and by Einthoven by means of the string galvanometer.

ately thereafter a deflection in the opposite direction, to prove that the distant pole of the muscle has now become active and negative.

While the ordinary type of galvanometer is sufficiently sensitive to perceive these electrical variations, its action is altogether too slow to follow them with accuracy. Although less sensitive, the strong galvanometer is more serviceable for these tests, because it possesses a much greater motility. There is one way, however, in which even the ordinary galvanometer may be made to indicate the current of action and that is, to cause its needle to be deflected first of all by the current of injury. Thus, if one of the non-polarizable electrodes is placed against the cross-section of the muscle, while the other is applied to its equatorial surface, the galvanometric needle will be forced to assume a fixed lateral position. If the distant non-injured portion of this muscle is now stimulated, the subsequent contraction of this region must give rise to a negativity which travels from here toward the other end of the muscle. As this contraction-wave and its negativity passes the plus lead of the current of injury, it reduces this positivity and causes the needle to swing toward and beyond zero. Inasmuch as the needle is deflected at this time in a direction opposite to that forced upon it by the initial current of injury, this phenomenon has frequently been designated as a "negative variation" of the primary demarcation current. This arrangement, therefore, permits the negativity accompanying the wave of contraction of muscle, to neutralize the positivity of the current of injury in the equatorial region of the muscle. Whether it will do that fully, depends upon the temperature and elastic tension of the muscle, but we might say that under favorable conditions the current of injury may equal 0.04 volt, while the current of action may amount to as much as 0.08 volt.¹ Clearly, the distance to which the needle will be deflected by the action current depends upon the strength of the latter, *i.e.*, upon the measure in which it is able to neutralize the initial current of injury.

The relationship existing between the wave of contraction and the current of action has been studied by photographing the variations of the galvanometric indicator together with the movements of two levers placed horizontally upon the surface of the muscle near the non-polarizable electrodes. It may be inferred that these two factors are very closely allied to one another, but the records obtained by the method just mentioned, indicate that the electrical changes antecede the movements of the corresponding lever by a fraction of a second. Two views may therefore be formulated, namely, (*a*) the electrical changes constitute the wave of excitation in consequence of which certain chemical alterations are instigated which eventually give rise to the shortening of the muscle, or (*b*) the electrical differences are the result of the chemical changes set off by the wave of excitation and are the forerunner of the mechanical effects. It is quite impossible at this time to decide this question one way or another.

¹ Piper, Pfüger's Archiv, cxxix, 1909, 145, and Jensen, *ibid.*, lxxvii, 1899, 137.

SECTION III

THE PHYSIOLOGY OF NERVE

CHAPTER XI

THE NEURON AND ITS CONDUCTING PATHS

The Neuron.—The entire nervous system is an aggregate of an infinite number of neurons which are held together by a nervous supporting framework or neuroglia, but many parts of it also contain cells showing a different histological character. Thus, it is found that the spinal cord and the cerebrum are enveloped by protective membranes which are made up of connective tissue, and contain in addition blood vessels and lymph channels for nutritive purposes. The element which we are chiefly interested in at this time is the neuron or nerve-cell. It consists of a cell-body and its processes, the latter being divided into dendrites and the axon or neurite.

In spite of the fact that the neuron is developed from a single embryonic unit, known as a neuroblast, the adult cell presents a great variety of forms. It may be pyramidal, oval, round, stellate or spindle-shaped, and its size may vary from 10–150 μ . The cytoplasm of each cell embraces a nucleus with its nucleolus, and a protoplasm which is granular in some places and striated in others. The latter contains numerous rounded bodies which stain deeply with methylene-blue and other dyes. These are the so-called Nissl's granules. Especially at the poles of the cell the cytoplasm is arranged in a distinct fibrillar manner, and is extended outward in the form of long processes, which, as has just been stated, are classified as dendrites and axons. The former divide very frequently and irregularly, and do not pass far away from the cell-body. Their terminals are generally beset with short stubby processes, known as the lateral buds or gemmules. They impart a peculiar uneven appearance to these processes.

Each cell-body usually gives rise to several dendrites but only to one axon. The latter is distinguished from the former by its much greater length, its uniform caliber, its smoothness and the greater directness of its course. It gives off very few branches, which are designated as collaterals, and exhibits a hyaline consistency. The dendrites, on the other hand, are not sharply differentiated from the cell-body unless they are long, when they may also acquire a hyaline appearance.

The Function of the Neuron.—We shall see later on that the cell-body is the nutritive center of the neuron, because its destruction entails the disintegration of all of its prolongations. Its purpose is to produce the nerve impulse and to convey it to distant parts. The arrangement in each neuron, however, is such that it can conduct in only one direction, namely from the dendrites to the axon. It possesses, therefore, a distinct polarity, the former prolongations being the avenues by which the nerve impulse is received and the latter the path by which it is conveyed to other parts. The general arrangement of the neuron, therefore, depends in a large measure upon the connections which it must establish with neighboring nerve-cells for functional purposes.

Neurons are usually designated as afferent or sensory and as efferent or motor. The former conduct impulses from the periphery to the center and the latter from the center to the periphery. Moreover, since several neurons of each type are always required to cover large distances, they are commonly arranged in series and are then differentiated from one another by characterizing them as neurons of the first, second, third, and so forth order. Just how many of them are required to unite two widely separated points of the nervous system differs greatly. Thus it is said that some of the efferent neurons of the spinal cord attain a length of 0.5–1.0 m., so that the distance between the cortex of the cerebrum and the foot may be covered by no more than two neurons, their relay station being situated in the anterior horn of the gray matter of the lumbar cord. On the afferent side, the path is less direct and hence, a more frequent relaying is made necessary. Thus, a sensory impulse generated in the foot, generally requires three or four consecutive neurons for its passage into the cerebrum.

Reflex Action.—The simplest relationship between these afferent and efferent neurons is presented by the so-called reflex circuit which permits of the occurrence of the simplest possible reaction, known as the reflex act. The responses executed with the help of

FIG. 62.—*M*, motor neuron; *S*, sensory neuron; *M*, motor end-organ; *S*, sensory end-organ; *A*, axis cylinder; *MS*, myelin sheath; *N*, neurolemma; *C*, collateral; *CB*, cell-body; *D*, dendrites; *Nu*, nucleus and nucleolus; *R*, sensory terminals.

nervous tissue, are divided into reflexes and voluntary reactions. The former are non-volitional and the latter volitional in their nature; hence, any action which is performed without the intervention of the will, is a reflex, while one requiring this amplification, is a voluntary reaction. As this topic will be dealt with in greater detail in a later chapter, it may suffice at this time to state that the production of a reflex necessitates the union of at least one sensory with one motor neuron. This union, however, is not effected by continuity, because the distributing terminals of the former merely lie in close contact with the receptive dendrites of the latter without becoming confluent.

FIG. 63.—REFLEX CIRCUIT.

SO, sensory end-organ, receptor; MO motor end-organ, effector; AN, afferent neuron; EN, efferent neuron; C, center; S, synapse.

The place where two neighboring neurons are in this way functionally united is known as a *synapse*. Most generally these synapses appear in the form of short arborizations of the sensory terminals around the bushy dendrite of the adjoining motor cell. In other cases, the distributing filaments are prolonged into the immediate vicinity of the neighboring cell-body which they surround in the form of a closely knitted reticulum. In still other synapses, the sensory terminals twine around the neighboring dendrite and invest it closely for some distance.¹ Attention should also be called to the fact that the sensory and motor neurons present certain general peculiarities which render them better adapted for their manner of conduction. Thus we find that the cell-body of the former generally occupies a central position, while that of the latter is situated near the end of the neuron. In fact, in certain sensory neurons, the cell-body lies at

some distance from the main conducting path, this condition being most clearly in evidence in the ganglia of the posterior spinal roots and those of the cranial nerves.

Under experimental conditions the reflex circuit may be stimulated at almost any point, the resulting impulse being propagated from here toward the axon terminals of the efferent neuron. Under normal conditions, however, the excitation is most generally received by the radicles of the afferent neuron which are modified into a sense-organ. A stimulus brought to bear upon the latter gives rise to an impulse

¹ Ramon Y. Cajal, *Histologie de syst. nerveux*, Paris, 1909, and Barker, *The Nervous System and Its Const.* Neurones, New York.

which travels over the afferent conductor to the motor cell, and from here over the efferent path into the terminals of the axon which are modified to form a motor end-organ in close alliance with the tissue effecting the reaction. Thus, it will be seen that a reflex circuit consists of a receptor, an afferent path, a center, an efferent path and an effector. In accordance with the different kinds of responses, the receptors and effectors present different structural and chemical peculiarities. For example, an afferent impulse may arise in the tactile corpuscles of the skin and eventually give rise to motion, the effector being formed in this particular case by the skeletal musculature. But the impulse may also be generated in the retina of the eye or in the organ of Corti and nevertheless lead to motion. This list might be extended almost indefinitely, because besides the ordinary responses of skeletal muscle, a large number of reactions are also brought about with the help of smooth muscle. In the latter group are to be placed the vasomotor and pilomotor actions, as well as the movements resulting in the domain of the stomach, intestine, ureter and bladder. Another group of very important sensory impulses produce secretory effects. But quite irrespective of the character of the reaction it should be kept in mind that any response executed in consequence of a sensory impression without the intervention of the will, constitutes a reflex.

The Structure of Nerves.—Each neuron is to be regarded as an elongated conductor, but naturally, neurons are generally combined into groups and do not appear singly. In the central nervous system an aggregation of the cell-bodies of several neurons is known as a nucleus and, in the peripheral system, as a ganglion. Furthermore, if a group of cells of this kind regulates a certain function, it is designated as a center. The former term, therefore, refers to an anatomical entity and the latter to a functional entity. The nerve-fibers passing away from these cell-bodies are generally bound together into bundles which are known as nerves. A nerve, therefore, represents a collection of nerve-fibers outside the central nervous system. It is formed in the following manner: the axon passes away from the cone-shaped projection of the cell-body, and soon becomes enveloped in a tubular membrane which constitutes the medullary or myelin sheath. In many cases, a second investment is found externally to this one which is known as the primitive sheath or neurolemma. Having acquired these sheaths, the axon, or, as it is now called, the axis-cylinder, becomes the nerve-fiber. Many of these are bound together to form a bundle, and many bundles to form a nerve. The individual fibers are supported by a fine stroma or endoneurium. The connective tissue investing the individual bundles of fibers, is known as the perineurium, and that surrounding the nerve as a whole, as epineurium. When a nerve divides, one or more of its bundles of fibers separate from its main trunk in the form of a branch. It frequently happens, however, that these branches do not pursue an independent course

but are interwoven with neighboring branches into an intricate network or plexus. When the individual nerve-fibers reach the end-organ, they subdivide into finer threads, or fibrils. In the vicinity of the end-organ the investing membranes disappear.

FIG. 64.—A, nerve fibers stained with osmic acid, showing axis cylinder, medullary sheath and neurolemma; B, medullated nerve fiber, showing nodes of Ranvier; $\times 660$ times. (Schäfer.)

The thickness of nerve-fibers varies between less than 2μ and more than 20μ . Those innervating the skeletal muscles are large and possess a diameter of about $14-19\mu$. While these differences are due very largely to the fact that some nerve-fibers are devoid of a medullary sheath, it must be remembered that even the axis-cylinders vary greatly in their thickness. Thus, it is easily apparent that the axons arising from the large ganglion cells of the anterior horn of the spinal cord, possess an especially large caliber. Nerve-fibers are either medullated or non-medullated

and may or may not be enveloped by neurolemma. A typical nerve-fiber consists of the following parts:

1. *The axis-cylinder* forms the central core of the fiber and about one-half of its total thickness. It appears as a dim or faintly granular thread which, under the influence of certain reagents, may become fibrillated. This peculiarity, as will be shown later on, is one of the important contentions of the fibrillar theory of nerve action. Each axis-cylinder pursues an unbroken course to the end-organ where it divides into a number of fibrillæ which may at times be closely interwoven with one another.

2. *The medullary substance* forms a close-fitting jacket around the axis-cylinder and consists of a network of neurokeratine, the meshes of which contain a fatty material. Under normal conditions it appears as a continuous layer of homogeneous substance which, after fixation or even while still in the body, splits up into segments possessing a length of about 1 mm. The indentations between these differ-

FIG. 65.—TRANSVERSE SECTION OF A NERVE (MEDIAN).

ep, epineurium; *pe*, perineurium; *ed*, endoneurium. (Landois and Stirling.)

ent segments are known as the nodes of Ranvier. They do not implicate the axis-cylinder. About midway between two neighboring indentations lies the nucleus, its long axis being directed parallel to that of the fiber. Immediately surrounding it is a layer of undifferentiated protoplasm which thus appears as small islands directly underneath the neurolemma.

3. *The neurolemma* is a transparent sheath of homogeneous material which retains a uniform thickness throughout, with the exception of the aforesaid nodes where it is augmented by cement substance and lies in direct contact with the axis-cylinder. Staining reagents are prone to enter these indentations and to progress from here along the axis-cylinder. As far as the relative amounts of these substances are concerned, it might be mentioned that the median nerve contains 63 per cent. of connective tissue, 28 per cent. of myelin and 9 per cent. of axis-cylinder (Ellison).

4. *The end-organs* to which the axis-cylinders are distributed, vary greatly in their structure as well as in their chemical composition. They are divided first of all into receptors and effectors. Among the former might be mentioned the retina of the eye, the organ of Corti of the internal ear, the olfactory cells, the taste buds, the cutaneous corpuscles for pressure, pain and temperature and the sensory spindles of striated muscle tissue. Probably the best known motor end-organ is the so-called end-plate of striated muscle. It appears as a low, conical or rounded

swelling at the junction of the axis-cylinder with the substance of the muscle-fiber. At this point the former loses its medullary sheath as well as the neurolemma, these envelopes becoming continuous with the sarcolemma of the muscle fiber. The plates themselves appear to be made up of fibrillar arborizations and possess a faintly granular or cloudy appearance. At the point of contact with the myoplasm, the arborization is more dense and presents a coarse granular appearance, forming what is known as the sole or bed of the end-plate.

The Chemistry of Nerves.—The composition of nerves has not been studied in great detail. Whatever data we possess have been derived very largely from analyses of the white matter of the cerebrum which, of course, is composed almost exclusively of nerve-fibers.

FIG. 66.—END-PLATES; CHLORID OF GOLD PREPARATION TO SHOW THE AXIS CYLINDERS AND THEIR FINAL RAMIFICATIONS OF FIBRILLE. $\times 170$. (Szymonowicz.)

The *proteins* are abundant and especially so in the axis-cylinder. One of these is a nucleoprotein which coagulates at 56 to 60° C. There are also present certain globulins. One of these coagulates at 47° C. and the other at 70 to 75° C. According to Halliburton,¹ the sciatic nerve is made up of 65.1 per cent. of water and 34.9 per cent. of solids of which the proteins furnish 29.0 per cent. The nerves of the cold-blooded animals begin to lose their irritability at about 40° C. and shorten more and more as the temperature rises.

The *lipoids* are also very abundant. They comprise phosphatides, such as lecithin and kephalin, galactosids and cholesterin or cholesterol in the following proportion:²

	Medullated nerve	Non-medullated nerve
Cholesterin.....	25.0	47.0
Lecithin.....	2.9	9.8
Kephalin.....	12.4	23.7
Galactosids.....	18.2	6.0

¹ Arch. of Neurology, ii, 1903, 727.

² Falk, Bioch. Zeitschr., xiii, 1908, 153; and Bang, Ergebn. der Physiol., vi, 1907, 131.

The lipoids are found chiefly in the myelin sheath, but as non-medullated fibers also contain them, they are not restricted to this particular part of the fiber. Medullated fibers, moreover, contain a much larger quantity of cerebrosids than the non-medullated, while the latter exceed in the lipoids, such as lecithin, kephalin and cholesterin. Ordinary fat is found in the epineurium, and gelatin in the connective tissue throughout the nerve. Very small amounts of creatin, xanthin, lactic acid, uric acid and urea have also been detected. The quantity of *inorganic salts* is small, amounting to only about 1.0 per cent. of the total solids. Potassium which is most abundant,¹ is said to play an important part in conduction.²

The Function of Nerves.—In the lower forms in which nervous elements are not present, the wave of excitation is propagated to other parts of the relatively small organism in a direct way, because protoplasm possesses not only the power of irritability but also that of conductivity. In a measure this is also true of the higher animals, but the conduction of the waves of excitation must here assume a somewhat different character, owing to the minute subdivision of the body into many colonies of cells which are frequently widely separated from one another. Previous to the discovery of the nerves it was believed that these impulses pursue a direct course in all directions through the different tissues, but we now know that long-distance conduction is effected solely with the help of nervous tissue which is especially suited for this function on account of its unusual irritability and conductile power. Conduction, therefore, presents itself first of all as an intracellular propagation of the wave of irritability and secondly, as a transfer of this wave to other colonies of cells elsewhere in the body. The result of this transmission of an excitation depends of course upon the character of the end-organ with which the nerve is connected, as well as upon the functional qualities of its center. Inasmuch as it is the function of the nerve to conduct impulses, the character of the energy evolved in consequence of it, must therefore be wholly dependent upon the effector with which it is functionally connected.

Irreciprocal Conduction.—The preceding discussion has brought out the important fact that the conduction in neurons is irreciprocal, *i.e.*, it takes place in only one direction. Thus, an impulse passes with greatest ease across the end-plate into the muscle, but not from the muscle into the axon and the cell-body. The same conditions prevail in the synapse, the conduction being from the axon of one neuron into the dendrites and cell-body of the next. This "Law of Forward Direction," as it has been called by Sherrington,³ possesses a physico-chemical basis, inasmuch as it has been shown that the different parts of the neuron are not built up of the same chemical substances. That this is so may be gathered from the fact that such agents as curare, nicotin, atropin and adrenalin do not affect the neuron uniformly throughout its substance but only in particular places. Curare, as has been pointed out previously, selects the motor-

¹ Macallum, *Ergebn. der Physiol.*, vii, 1908.

² Macdonald, *Proc. Royal Soc.*, lxxvi, 1904-05, 322.

³ *Proc. Royal Society, London*, lii, and following.

plates for its point of attack, while nicotin paralyzes the dendritic processes of the cell-body and atropin the terminals of the axon. Secondly, it is a well-known fact that the time which an impulse requires for its passage through a neuron, is largely taken up by its journey through the cell-body and the end-plate. In the latter, for example, the delay is appreciable, amounting to more than one thousandth of a second. Thirdly, it has been demonstrated that the fatigue of muscle, resulting from excessive indirect stimulation, makes itself felt first of all in the end-plate and not in the nerve-fiber nor in the muscle tissue. These and other facts unmistakably point toward the presence of a third substance which, strictly speaking, is neither nerve tissue nor muscle tissue but a modification of the former. It is usually designated as the *intermediary or receptor substance*. It is conceivable that the constituents of this substance arrange themselves as electrolytes in a way to permit of the passage of the excitation in only one direction. This is true of the end-plate as well as of the synapse.

The Function of the Different Parts of the Nerve.—The transmission of the wave of excitation is effected by the axis-cylinder, or rather, by the neurofibrils of which it is composed. The latter, as has previously been shown, ramify throughout the cytoplasm and form connections between the different poles of the cell-body and its processes.

The myelin sheath is said to possess a protective, insulating and nutritive function. The first assertion finds substantiation in the fact that the medullary sheath is composed of a spongy network containing a soft fatty material. Thus, if a nerve-fiber is torn, droplets of a substance will be seen to ooze out which exhibit a double outline similar to that of the nerve-fiber itself. If subjected to osmic acid, these globules stain black, owing to the reduction of the osmium. Moreover, the cross-section of a fiber invariably appears as a heavy dark ring surrounding a light, faintly stained central area. It is also a well-known fact that ether and other solvents are capable of removing this fat at least in part so that the fiber assumes the appearance of a round tubular space surrounding the axis-cylinder. The latter may then be stained with carmin and other dyes to render it more conspicuous. It seems, however, that the contention that the myelin sheath supports and protects the axis-cylinder in a mechanical way, cannot be emphasized especially, because the non-medullated axons of the sympathetic system show perfect conduction. Moreover, axons are never medullated throughout their entire extent but lose their sheath near the cell-body as well as near the end-organ. In the third place, while the cerebrospinal nerves are ordinarily in possession of such a covering, they do not attain it simultaneously but at different periods of embryonic life. In fact, in some animals, such as the rat, this sheath is not developed until several days after birth. Meanwhile the newborn animal shows perfectly coördinated movements.¹

¹ Donaldson, Jour. of Comp. Neurology, xx, 1910, 119; and Ambronn and Held, Arch. für Anat. und Physiol., 1896, 208.

The same arguments may be advanced against the view that the myelin sheath serves as an insulator to prevent the overflow of an impulse from one axis-cylinder to another. So far no definite proof has been furnished for the contention that the non-medullated fiber conducts less efficiently than the medullated. It is frequently held, however, that the loss of coördination resulting in the course of multiple sclerosis of the cord, is due to the destruction of the myelin sheaths of these fibers, because their axis-cylinders appear to be perfectly normal. In general, however, it is true that the wave of excitation is conducted without it spreading to neighboring fibers by contact. Isolated conduction, therefore, is the rule.

The third contention, that the myelin sheath serves as a nutritive medium for the axis-cylinder, is based upon the following data. It has been found that its thickness varies directly with the caliber of the axis-cylinder, and that the axons of the projection system of the cerebrum are the thickest of all. Moreover, inasmuch as staining reagents find ready access to the axis cylinder through the different indentations at the nodes of Ranvier, it has been supposed that the nutritive substances select the same course. It has also been observed that the stimulation of a nerve is followed by certain structural changes in the myelin sheath, consisting in a widening of the meshes of its neurokeratin framework.¹ Medullated fibers are also said to be more irritable and to possess greater recuperative powers than non-medullated. None of these facts, however, is sufficiently definite to constitute an actual proof of the aforesaid view. In addition, it might be mentioned that the axis-cylinder and the myelin sheath have really a separate origin, because the former is an outgrowth from the cell-body, and the latter, from the mesoblastic cells surrounding the axon. This histogenetic peculiarity is also betrayed by the changes which an adult nerve-fiber undergoes in the course of degeneration and regeneration. The latter prove conclusively that the axis-cylinder is nourished from the cell-body, while its investments derive their nutritive material directly from neighboring blood-vessels.

The neurolemma is generally regarded as a supporting and protecting membrane and plays an important part in the degeneration and regeneration of nerve tissue. The view that it is also insulating and nutritive in its function could be met with the objections enumerated previously.

Degeneration of Nerve.—The nerve-fiber retains its normal appearance and function only as long as it remains in connection with the cell-body. When its continuity is broken by cutting, crushing, heating or other means, the fiber loses its irritability and conductivity and undergoes very characteristic retrogressive changes. Directly after the injury, however, its excitability is temporarily increased and especially at the seat of the trauma, owing, in all probability, to the

¹ Strübel, Pflüger's Archiv, cxlix, 1912, 1.

development of a current of injury. At this time a gradual retrogression sets in which terminates eventually in a complete loss of irritability.¹ The interval of time required for the development of these changes varies in accordance with the type of the animal, the condition of the nervous tissue and the severity of the lesion. In warm-blooded animals, for example, the excitability is lost in from 2 to 4 days, while in cold-blooded animals it generally takes a much longer time. For the sciatic nerve of the frog this interval is usually given as 33 days, although it may be as long as 3 or 4 months. Evidently, this difference is dependent upon the nutritive condition of the animal and the temperature, because the degeneration sets in much sooner during the summer and frequently progresses at this time with a speed equal to that observed in the mammals. In young and vigorous animals its progress is more rapid. It should be remembered, however, that the development of these changes necessitates the complete separation of the fibers from the cell-body, because if they are merely divided and their ends left in contact with one another, the degeneration is prone to assume an abortive character. The irritability then fails to decrease and besides, the morphological changes do not develop with any degree of definiteness.

Degeneration is classified as primary, secondary, and tertiary. The *primary* type involves the nerve-fibers at the seat of the injury and affects solely those internodal segments which have been directly exposed to the trauma. Beginning at this point, the degeneration first progresses outward in the direction of the conduction of these axis-cylinders until it finally involves their distalmost branches. This marked implication of their peripheral stumps constitutes *secondary degeneration*. As far as the efferent paths are concerned, it may be inferred that their destruction must render the effector functionally useless, because its separation from the cell shuts out those central discharges which normally keep it in tonus and activate it. Thus, while the degeneration of nerve really ceases in the end-plate, it also implicates in an indirect way the tissue with which it is in functional relation. The latter then suffers a disarrangement of its metabolism in consequence of the loss of the usual efferent impulses. Thus it may be observed that the destruction of a musculomotor nerve is invariably followed by atrophic changes in the muscle innervated by it. It is noted that the muscle fibers decrease in thickness, and that their cross-sections lose their sharp contours and fibrillar appearance. They eventually assume a hyaline appearance and become widely separated from one another by infiltrated fat. Very similar changes result in afferent paths. The direction of the degeneration in them may be either centrifugal or centripetal in accordance with the location of the cell-bodies.

In either case the destruction of the conducting path must lead to an isolation of the cell-body and its dendrites, thereby rendering the

¹ Waller, Müller's Archiv, 1852, 392.

latter functionally useless. This enforced inactivity causes the cell-body to lose its irritability and to undergo very characteristic morphological changes which present themselves as an initial turgescence and final atrophy of its cytoplasm and nuclear material. The Nissl's granules become indistinct and finally disappear so that the cytoplasm assumes a more homogeneous character. It is to be emphasized, therefore, that the degeneration begins at the seat of the trauma and advances from here in a peripheral as well as in a central direction. It involves first of all the entire distal end of the nerve and later on also its central stump, inclusive of the corresponding cell-bodies and their dendrites. The degeneration progressing in a central direction, is commonly designated as *retrogressive degeneration*. Lastly, it is to be noted that these retrogressive changes do not stop at the next synapse, but also implicate those neighboring neurons which are in functional relation with the neuron primarily affected by the injury. The cause of this retrogression must again be sought in the inactivity forced upon the correlating neurons by the trauma to one of their series. This type of degeneration may be characterized as *tertiary*, because it is not the direct result of the lesion, but develops only in the course of time in those neurons which formerly acted in harmony with the injured neuron.

We have seen that neurons are arranged in such a manner that their axons conduct either in an efferent or afferent direction. Inasmuch as the degeneration first involves that segment of the fiber which has been disconnected from the cell-body, the morphological changes must advance along an efferent fiber in a direction from the center toward the periphery. In an afferent fiber conditions are not so simple. The cell-body is situated in between its processes. The degeneration, therefore, may affect either its distal or its central processes. This statement will be more easily understood if a brief reference is made at this time to the so-called *Wallerian law of degeneration*. It is a well-known fact that the anterior roots of the spinal cord are formed by axons which are derived from large ganglion cells situated in the corresponding horn of the gray matter. These axons, therefore, conduct toward the periphery and are wholly efferent or motor in their function. For this reason, a division of this root must be followed by a degeneration which progresses outward from the level of the cut until all the terminals have become involved (Fig. 67, I). The central stump of this root as well as the corresponding cell-bodies and their dendrites, will be affected in the course of time by retrogressive degeneration. The posterior root of the spinal cord, on the other hand, is made up of axons which arise in cells situated in the so-called spinal ganglia. Their function is afferent or sensory, and hence, their direction of conduction is from the periphery to the center. This fact implies that the division of this root must give rise to a degeneration involving the end still connected with the cord (Fig. 67, II), whereas its other end which has remained in contact with the ganglion, under-

goes merely a gradual retrogression. The peculiar distribution of these fibers also permits of a third cut being made, namely, at a point distally to the spinal ganglion. In the latter case, the degeneration involves the distal axons, leaving the entire posterior root intact until subsequently affected by retrogressive changes (Fig. 67, III).

Very similar conditions prevail inside the central nervous system. Thus, it may be noted that the anterior pyramidal tracts of the spinal cord are formed by axons derived from cells in the motor area of the cerebral cortex, whereas the posterior columns are made up of axons,

FIG. 67.

FIG. 68.

FIG. 67.—THE COURSE OF THE DEGENERATION IN THE ROOTS OF THE SPINAL CORD.

AR, anterior root; PR, posterior root; I, division of anterior root; II, division of posterior root centrally to ganglion; III, division of posterior root distally to spinal ganglion. The degenerated fibers are indicated in black.

FIG. 68.—DIAGRAM TO ILLUSTRATE THE DIRECTION OF DEGENERATION IN SPINAL NEURONS.

The degenerated portion is indicated by dotted lines.

the cell-bodies of which lie either in the spinal ganglion or at a low level of the cord. The former are motor and the latter sensory in their function. Consequently, a division of the spinal cord, say, at the level of the first thoracic vertebra must be followed by an outward degeneration of the pyramidal tracts and an inward degeneration of the posterior columns. The former is generally called *descending* and the latter *ascending* degeneration.

The Morphological Changes of Degeneration.—The foregoing discussion must have shown that the cell-body is the nutritive center

of the neuron. As far as the dendrites and axons are concerned, it is conceivable that they are nourished by neuroplasmic streams from the cell-body, whereas the nutritive supply of the investments is derived from neighboring blood-vessels and lymphatic channels. The metabolism of both, however, depends upon the functional capacity of the neuron as a whole. The cell-body, therefore, constitutes the trophic center of the neuron and the element chiefly concerned in this function is the nuclear material. This deduction may be justified by the analogy that the survival of a cell depends upon the preservation of its nuclear substance. Thus, if a cell is divided several times, its different fragments must soon disintegrate, unless a sufficiently large mass of the nucleus have been apportioned to each of them.

In describing the histological alterations occurring in a disintegrating neuron, attention should first be called to the degeneration involving the fiber separated from the cell-body and secondly, to the retrogressive changes affecting the cell-body and its dendrites. Concerning the former it should be noted that the primary degeneration remains confined to the seat of the injury and advances only as far as the second or third node centrally and distally to it. The stretch of fiber so affected measures no more than 3.0 mm. in length. From here this process spreads so rapidly that it becomes practically simultaneous throughout the distal stump.¹ A typical Wallerian degeneration is initiated by a loss of irritability which is associated with a turgescence and a fragmentation of the axis-cylinders. These changes develop two or three days after the injury.² They are quickly followed during the next day by a fragmentation of the myelin sheath. The latter breaks up into ellipsoidal segments and then into smaller drops, each of which contains a short stretch of the axis-cylinder appearing as a complex of colorless granules. Naturally, these structural alterations of the myelin substance are associated with certain chemical changes which betray themselves by its different staining qualities.³ This particular phase of the degeneration is followed by a period during which much of the material thus formed is gradually absorbed so that at the end of one month the fiber is practically without its medulla. Meanwhile, the nuclei of the neurolemma have greatly increased in number and have become invested by a layer of protoplasm which thus partially occupies the place of the absorbed myelin. This structure is known as the "band fiber." Its appearance is of course very different from that of a normal nerve-fiber and there is sufficient evidence at hand to prove that it is non-conductile.

In this connection it should also be mentioned that the distal and central stumps in the immediate vicinity of the lesion are frequently beset with neurofibrillar outgrowths from the axis-cylinder. These rami, however, cannot be considered as indications of regeneration,

¹ Ranson, *Jour. Comp. Neur. and Psych.*, xxi, 1912, 487.

² Bethe and Mönkeberg, *Arch. für mikr. Anat.*, liv, 1899, 135.

³ Mardi's method of staining with osmium after treatment in a chrome solution.

because they again disappear in from three to eight days after the injury and even if they are well protected by a tubular investment of fascia. The degeneration, therefore, ceases with the formation of the band fiber, a functionally inert strand of protoplasm. The central stump, as has been stated above, degenerates in a typical manner only for a distance of two or three nodes of Ranvier and hence, only those segments are involved which have been directly exposed to the trauma.

In addition, it has been noted that the cell-body of this neuron, as well as such neurons as are in functional relation with it, undergo certain changes which are arranged collectively under the name of retrogressive degeneration. It is readily conceivable that an injury to a chain of neurons must subject all of them to a certain inactivity which is accompanied by a disturbance of their metabolism. The cell-body becomes swollen and finally atrophies, this decrease in the quantity of its cytoplasm being associated as a rule with an irregularity in the contour of the nucleus and a change in its position to a place nearer the surface of the cell. The chromatin material gradually disappears so that the staining power of the cell becomes much diminished,¹ and the more so, because this chromatolysis also affects the Nissl's granules. It has also been shown by Dickinson² that many of these cells become vacuolar and may indeed be completely destroyed, but these retrogressive changes require a relatively long time for their completion.

The Morphological Changes of Regeneration.—The regenerative processes set in whenever the continuity of the neurons is reestablished, provided, of course, that not too long a time has elapsed since the injury. Thus, if a nerve is cut and its two ends are again brought into contact immediately, the resulting changes are so fleeting that they can scarcely be regarded as typifying Wallerian degeneration. Concurrently, it may be assumed that a degeneration of long standing can only be remedied by a regeneration occupying a correspondingly long time.

In accordance with the view that the neuron is not only the structural but also the functional unit of the nervous system, it is commonly believed that the regeneration of the peripheral ends of the different fibers can only be effected by outgrowths from the axis-cylinders of the central stump (Ranvier). These neuroplasmic proliferations are said to seek the old neurolemmal sheaths and to continue through them into the end-organs. Opposed to this view is the one which holds that a functional unit necessitates the presence of a number of neurons arranged in series. In accordance with this conception, it is held by Bethe and others that the neurolemma is composed of the remnants of the neuroblasts from which the nerve-cells have originated. The cutting of a nerve, therefore, would permit these elements to assume their former characteristics and to give rise to regenerative changes in the different fibers. While several facts might be mentioned in support

¹ Ranson, *Jour. of Comp. Neur. and Psych.*, xvi, 1906, 265.

² *Jour. of Anat. and Physiol.*, iii, 1869, 176.

of the second view, it will be shown later on that the former conception of regeneration is the more correct.

Assuming, therefore, that the regeneration of the fibers results in consequence of a central proliferation of neuroplasmic material,¹ the question may be asked whether this outgrowth takes place from the axis-cylinder or from its investments. Briefly stated, it appears

FIG. 69.—HISTOLOGY OF A DEGENERATING NERVE FIBER. (Howell.)

that this process begins with a hyperplasia of the neurolemma at the site of the section of the nerve, and while the central as well as the peripheral stumps participate in this reaction, the principal part is played by the former.² The cytoplasm surrounding the nuclei of this locality, is rapidly increased in amount, as is also the number of

FIG. 70.—EMBRYONIC FIBERS IN A REGENERATING NERVE. (Howell.)

the nuclei themselves. In this way numerous protoplasmic streamers are developed which become well differentiated in the course of from four to six days and progress into the distal stump, where they form thickened bands of cytoplasm within the neurolemmal sheaths. The axis-cylinders of the central stump follow along these protoplasmic bridges and thus close the defect. In many cases they may even be

FIG. 71.—A NEWLY DEVELOPED FIBER IN A REGENERATING NERVE FIBER. (Howell.)

seen to penetrate the cicatricial tissue at the site of the injury. To begin with, these axons are non-medullated but acquire a myelin sheath in the course of from five to six weeks (dog)—provided, of course, that they were medullated previously. This medullation begins proximally and progresses toward the periphery.

A continuity having been established in this way, the corresponding cell-bodies and their collaborating neurons gradually regain their

¹ Purpura, *Archivio ed atti della Soc. ital. di Chirurgia*, 1909 and 1911; also see: Perroncito, *Mem. del R. Ist. Lombardo di Sc. et Lett.*, xx, 1908.

² Kirk and Lewis, *Johns Hopkins Hosp. Bull.*, xxviii, 1917.

normal appearance and again become functional. It might probably be mentioned that this regeneration does not always lead to a reunion of the same axis-cylinders; in fact, a union may be effected between the central and distal stumps of two different motor nerves or their branches. Quite similarly, a sensory nerve or a segment thereof may be brought into functional connection with a motor nerve. Purpura, for example, has obtained good functional results in cases of paralysis of the face by joining the distal end of the facial nerve with the central end of the spinal accessory. In animals the latter nerve has also been united with the vagus nerve, this crossing enabling an ordinary musculomotor nerve to produce an inhibition of the heart.

Very important evidence favoring this centro-peripheral manner of regeneration, has been presented by Harrison.¹ It has been shown by this investigator that the excision of the neural crest in the larvæ of amphibians, from which the cells of Schwann are derived, does not hinder the development of the axis-cylinders but prevents their acquiring medullary sheaths. It has also been demonstrated that nerve-cells send out axis-cylinders when immersed in a favorable nutritive medium and that nerve-fibers are generated by pieces of cerebellum and spinal ganglia when kept in a culture of clotted plasma. Many of these axon processes attain a length of 0.5 mm. in the course of 48 hours.

CHAPTER XII

THE PHENOMENA OF CONDUCTION IN NERVE

Irritability and Conductivity.—Under normal conditions the wave of excitation arises at one pole of the neuron and traverses it in a definite direction, either afferently or efferently. Under experimental conditions, on the other hand, it is possible to bring the stimulus to bear upon it at almost any point, *i.e.*, either upon its cell-body, its axon or its end-organ. But the reaction remains the same in all cases, a motor effect resulting from the excitation of a motor nerve and a sensation from that of a sensory nerve. The structural element primarily concerned in this transmission of the wave of excitation is the fibrillated axis-cylinder of the nerve-fiber and its ramifications inside the cell-body.

It is possible to differentiate between the irritability and conductivity of nerve in the following manner: A muscle-nerve preparation (*M*) is placed horizontally upon a glass plate, the nerve (*N*) being drawn through a small glass chamber (*D*), which in turn is connected with a Kipp apparatus (*C*). One pair of electrodes are adjusted to the nerve inside this chamber (at *A*) and another pair outside of

¹ Harvey Lectures, New York, 1909, 199.

it (at *B*). A pole changer is made use of so as to be able to divert the current in the shortest possible time. Provided that the nerve has not been injured, the muscle reacts when stimulated at either point. If carbon dioxide is now permitted to flow into this chamber, the stimulation at *A* becomes ineffective, while that at *B* persists. This procedure may be repeated a number of times, but the excitability of the nerve returns very soon after the carbon dioxide has been removed from the chamber. It seems, therefore, that small quantities of this gas destroy the irritability of the nerve, but do not affect its conductivity, and hence, these two properties may be said to occur independently of one another.¹ If vapors of alcohol are now introduced into this chamber, the nerve loses even its conductivity, as is evinced by the fact that the stimulation at *B* is now quite ineffective. In a similar way, it may be shown that ether and chloroform diminish the irritability as well as the conductivity, but the former more intensely than the latter. Furthermore, it may be observed that when the effect of these depressants wears off, the conductivity is reestablished more rapidly than the irritability.

The Direction of Conduction.—

In studying the different phenomena connected with the conduction of nerve impulses, it is customary to make use of a musculomotor nerve which is still attached to its muscle. Nerves exhibit no visible signs of their activity, *i.e.*, they do not liberate mechanical energy nor do they generate heat or electricity in amounts sufficient to be recognized by means of our unaided sense-organs. In this case, therefore, the muscle serves the purpose of an indicator of the activity of the nerve, because under normal

conditions every excitation of the latter gives rise to a muscular contraction. But naturally, before this effect can make itself felt, the wave of excitation must have been transmitted from the seat of the stimulation to the motor end-organ. Conduction, therefore, is the specific function of nerve, its property of irritability enabling the stimulus to produce certain chemico-physical changes which are then propagated onward in the form of a wave of excitation or nerve impulse. It must also be evident that any other motor mechanism or even a sensory nerve, may be employed for these experiments. In the latter case, however, it is necessary to arrange the sensory nerve in such a way that it can give rise reflexly to a motor effect, because this is the most convenient way of proving its activity.

The preceding discussion pertaining to the serial arrangement of

FIG. 72.—CONDUCTIVITY AND IRRITABILITY OF NERVE.

M, muscle; *N*, nerve; *D*, glass chamber; *C*, Kipp apparatus; *A* and *B*, electrodes inside and outside the gas chamber.

¹ Grünhagen, Pflüger's Archiv, vi, 1872, 181; and Luchsinger, *ibid.*, xxiv, 1881, 347.

the motor and sensory neurons, must have shown that the wave of excitation is propagated along nerve-fibers in a particular direction, namely from the receptor to the effector. Thus, afferent fibers conduct normally in a centripetal direction, and efferent fibers in a centrifugal direction. This constitutes the so-called *law of forward conduction*. An entire nerve, on the other hand, need not be purely afferent or efferent in character, but may be composed of both types of fibers. In the latter case, it is designated as a mixed nerve. Its power of conduction, however, is not interfered with, because a spreading of its impulses from fiber to fiber, is not possible under normal conditions. Mixed nerves, therefore, may convey centripetal and centrifugal impulses at the same time.

If the substance of a unicellular organism is stimulated, the wave of excitation proceeds from the seat of the stimulation in all directions. In a similar way, it may be noticed that the application of a stimulus to the center of a single muscle-cell is followed a moment thereafter by a contraction of its two ends. The results obtained with nerve-fibers are practically the same, but naturally, this statement applies only to nerves which are tested under experimental conditions. Thus, the stimulation of a motor nerve manifests itself solely by a peripheral reaction in spite of the fact that the wave of excitation is also propagated in a centripetal direction. Quite similarly, the excitation of a sensory nerve cannot betray itself by a reaction in the receptor, but only by some central effect which in time may lead to a reflex motor response. It is evident, therefore, that the law of forward conduction may be changed by experimental means into a law of double conduction. The direction of the conduction, however, is not dependent upon differences in the substance of the nerve-fiber, but solely upon its central and peripheral connections. The irreciprocity of conduction, as we have previously seen, is wholly determined by the conditions existing at the poles of the neuron.

The fact that the nerve impulse may be propagated in both directions is most clearly proven by the following experiment (Fig. 73) devised by DuBois-Reymond.¹ Each end of a long stretch of nerve is connected with the poles of a galvanometer. On stimulating the nerve about midpoint between these instruments, it is noted that both needles are deflected. For the present this phenomenon need not be explained further than to state that the passage of a nerve impulse gives rise to an action current which betrays itself by a galvanometric negativity. Inasmuch as this negative variation appeared at both ends of the nerve, it must be concluded that the wave of excitation has progressed in this case in a central as well as in a peripheral direction. It is also to be noted that this result may be obtained not only with mixed nerves, but also with pure afferent or efferent nerves. Gotch and Horsley² have modified the foregoing experiment by adjusting a galvanometer to the distal end of one of the divided anterior roots of the sciatic nerve of the cat, and by subjecting the distal trunk of this nerve to repeated stimulations. The centrifugal conduction was manifested in this case by the contraction of the leg muscles and the centripetal conduction by the deflection of the needle of the

¹ Thierische Elektrizität, ii, 1849, 587.

² Philos. Transactions, 1891.

galvanometer. To adjudge this result correctly, it must of course be remembered that the anterior roots of the cord are motor in their function; *i.e.*, they conduct under normal conditions in a centrifugal direction. Double conduction for the afferent fibers was proved by stimulating the posterior root of the sciatic nerve and observing the deflections of a galvanometer adjusted to the central end of the peripheral portion of this nerve. The posterior roots of the spinal nerves are sensory in their function and conduct under normal conditions in a centripetal direction.

FIG. 73.—CONDUCTION IN BOTH DIRECTIONS IN NERVE.

N, nerve; *S*, point of stimulation; *A* and *B*, galvanometers upon the two ends of the nerve.

Another method of proving double conduction in nerve has been devised by Kühne¹ (Fig. 74). It has previously been stated that several of the long muscles, such as the gracilis and sartorius, receive their nerve supply at a point about midway between their two extremities. The nerve entering here divides into two principal branches, which innervate the upper and lower ends of the muscle respectively. If the muscular continuity is now broken by a transverse cut into the tip of the triangle formed by these branches (*C*), the upper and lower ends of the muscle (*A* and *B*) will be practically isolated from one another save for the bridge of

FIG. 74.—CONDUCTION IN BOTH DIRECTIONS IN GRACILIS MUSCLE.

A and *B* segments of gracilis muscle divided by cut *C*; *S*, point of stimulation; *N*, motor nerve and its branches.

nerve-tissue. If the distalmost filaments of one of the branches of this nerve are now stimulated (*S*), the muscular contraction immediately ensuing does not remain confined to this half of the muscle (*A*) but also involves the other half (*B*). This fact leads us to infer that the excitation advances first of all in a centripetal direction over the fibers of the corresponding branch (*A*) and then spreads over the normally centrifugal fibers to the distant muscle-strip *B*. Thus, the normally efferent fibers innervating the end *A*, are temporarily converted into afferent fibers. In order to meet the possible objection that this result may be caused by a direct spreading of the electrical current from *A* to *B*, the stimulation may be

¹ Archiv für Anat. und Physiol., 1859, 595.

effected by simply pinching the distal filaments of the nerve with forceps or by cutting across them with the scissors.

A very similar relationship exists in the electrical organ of *Malapterurus*.¹ Inasmuch as its individual membranous plates are innervated by the branches of a single motor nerve (Fig. 75), the mechanical stimulation of the terminals in a single plate must invariably be followed by a discharge of the entire organ. Clearly any impulse arising peripherally in one of these plates (*D*), can only be transferred to the adjoining plates (*AB* and *C*) at the next bifurcation, and hence, the impulse must first ascend along the normally efferent branch before it can spread in a centrifugal direction to the other parts of the organ. This peripheral transfer of impulses is made possible by the fact that the individual axis-cylinders of the motor fibers divide when in close proximity to the end-organ and send their fibrillar components in different directions into the tissue.

FIG. 75.—CONDUCTION IN BOTH DIRECTIONS IN THE ELECTRIC ORGAN OF MALAPTERURUS.

N, motor nerve and its branches, leading to plates *A B C* and *D*; *S*, stimulation at *D* produces discharges of entire organ.

Consequently, it is not necessary that the reversed impulse be transferred to a neighboring axis-cylinder, because it can reach its destination through the fibrillae of the same axis-cylinder. It will be seen, therefore, that conduction in both directions is not contrary to the law of isolated conduction.

Different investigators have also sought to prove double conduction by the establishment of a primary union between the central and distal stumps of different sensory and motor nerves. Thus, it has been shown by Bidder (1865) that a union between the distal end of the hypoglossal (motor) and the central end of the lingual nerve (sensory) eventually permits us to effect movements of the tongue by stimulating the sensory lingual nerve. In a similar way, Budgett and Green² have succeeded in cutting the left vagus nerve between its ganglion and the cranium and in uniting the peripheral stump of this nerve with the peripheral end of the hypoglossal. Some months later the muscles of the tongue could be made to contract by stimulating the peripheral end of the vagus. In this connection brief mention should also be made of the well-known experiment of Paul Bert³ purposing the formation of a primary union between the tip of the tail of a rat and the subcutaneous tissues upon the dorsal aspect of its body. The process of healing having been fully completed, the tail was then cut off near its base. Inasmuch as the stimulation of the former base of the tail still gave rise to sensations of pain, the conclusion seemed justified that nerve-fibers conduct centripetally as well as centrifugally. In all these experiments, however, it must be taken into account that the cutting of nerves is followed by degeneration which in turn is succeeded by the formation of new axis-cylinders. For this reason, it cannot be held that the inversion of a part actually leads to an inversion of the nerve-fibers or to reversed conduction. These experiments, therefore, cannot be said to be well adapted for proving double conduction.

The Speed of Conduction in Nerve.—Inasmuch as the passage of the wave of excitation is not associated with visible changes, it was thought at first that the rate of its progression, in analogy with that of

¹ Babuchin, *Archiv für Anat. und Physiol.*, 1877, 262.

² *Amer. Jour. of Physiol.*, iii, 1899, 115.

³ *Compt. rend.*, lxxiv, 1877, 173.

light, is immeasurable. But this view, which was first expressed by Johannes v. Müller, in 1844, could not be maintained for any length of time, because already in 1850 v. Helmholtz¹ devised a method which gave fairly accurate results. In brief, it consisted in determining the time elapsing between the application of an electrical stimulus to the nerve of a nerve-muscle preparation and the moment when the resulting contraction of the muscle caused the circuit of a galvanic battery to be broken. Very clearly, however, this interval included not only the time occupied by the passage of the excitation to the muscle, but also the time of contraction of the muscle itself. A few months later Helmholtz devised a second method which is not only much simpler but also much more accurate than the one just mentioned (Fig. 76).

FIG. 76.—SPEED OF THE NERVE IMPULSE.

M, muscle and nerve connected with writing lever *W* and two pairs of electrodes *N* and *F*. The wires from inductorium *J* are connected with the pole change *P*, so that the nerve may be stimulated either near to or far away from the muscle.

A nerve-muscle preparation (*M*) is connected with a writing lever (*W*) in the manner described in one of the earlier chapters. The nerve is then stimulated either at a point far away from the muscle (*F*) or close to it (*N*). In each case, the contraction of the muscle is recorded upon a swiftly revolving kymograph, above the record of a tuning fork vibrating in hundredths of seconds and the record of an electromagnetic signal indicating the precise moment of stimulation. If the lengths of the latent periods of these contractions are compared with one another, it will be found that those obtained by stimulating the nerve far away from the muscle (*F*), are appreciably longer than those recorded by stimulating the nerve near the muscle (*N*). The difference between these latent periods corresponds to the time consumed by the wave of excitation in its passage from *F* to *N*. This distance having been determined with the ruler, the time may then be calculated

¹ Monatsber. d. Berliner Akad., 1850.

which the impulse requires for its journey through this particular stretch of nerve.

The values which Helmholtz obtained varied between 24.6 and 38.4 m. in a second, the determinations being made at temperatures varying between 11° and 21° C. At the average temperature of the room, the velocity for the musculo-motor nerves of the frog may therefore be said to be about 28 m. in a second. By recording the contractions of the muscles of the thumb during stimulation of the median nerve at two widely separated points, Helmholtz and Baxt¹ have also determined the speed of conduction in human nerves. They found it to be about 34 m. in a second. In the lower animals, the rate of conduction varies considerably and even in different nerves of the same animal. Fredericq and Vandervelde,² for example, give the value of 6 to 12 m. in a second for the nerve of the claw of the sea-crab, and v. Uxküll,³ the value of 0.4 to 1 m. in a second for the nerve of the mantle of cephalopods. In the nerve plexus of the heart of *Limulus*, Carlson⁴ found the speed to be 0.4 m. in a second and in the pedal nerve of *Limax* 1.25 m. in a second. The non-medullated olfactory nerve of the pike conducts at the rate of 0.6 to 0.9 m. in a second.⁵ According to Chauveau,⁶ the vagus fibers innervating the smooth musculature of the esophagus of mammals, conduct with a velocity of 8.2 m. in a second and those innervating the striated musculature of the larynx, at the rate of 66.7 m. in a second. The non-medullated fibers, therefore, conduct less rapidly than the medullated; moreover, conduction through the central nervous system is effected at a slower rate than through the peripheral nerves. It must also be evident that the speed of the wave of excitation in nerve is much less than that of certain physical energies. Thus, sound travels with a velocity of 332 m. in a second, whereas light attains a speed of 332 million meters and electricity a speed of 464 million meters per second.

In recent years additional light has been thrown upon this topic by the use of the string galvanometer. It may be stated at this time that the passage of the wave of excitation is associated with an electrical variation which may be accurately followed by a quickly reacting galvanometer. Piper⁷ employed the median nerve which he stimulated either at the elbow or in the axilla. The precise moment of entrance of the excitation into the distant muscles was indicated by a string galvanometer adjusted in such a way that it registered the initial phase of the action current in these muscles. Knowing the length of the stretch of nerve intervening between the axilla and the elbow, and also the time elapsing between the moment of the application of the

¹ Monatsb. der Berliner Akad., 1870.

² Bull. de l'acad. de Belgique, C. r., 1875, 91.

³ Zeitschr. für Biologie, xxx, 1894, 550.

⁴ Am. Jour. of Physiol., xiii, 1905, 217.

⁵ Nikolai, Pflüger's Archiv, lxxxv, 1901, 65.

⁶ Acad. Scienc., lxxxvii, 1878.

⁷ Pflüger's Archiv, cxxiv, 1908, 591.

stimulus at either point and the deflection of the string, the velocity of the wave could easily be calculated. If stimulated in the axilla, the deflection followed after an interval of 0.00578 second, and if stimulated at the elbow, after 0.00442 second. As the distance between these two points amounts in most persons to 160–170 mm., the wave must have progressed with a velocity of from 117 to 125 m. in a second.

Factors Altering the Speed of Conduction in Nerve.—The fundamental condition for conduction is the anatomical continuity of the nerve-fibers. If this has been broken in any way whatever, the excitation must fail to reach the distant segment. An incomplete block may be established in various ways, for example, by compression, or by crushing and stretching. Conduction then reappears gradually. It may also be observed that the sensory fibers are somewhat less resistant than the motor fibers. Thus, if pressure is brought to bear upon the ulnar nerve at the elbow, the region supplied by it “goes to sleep,” but while this state is characterized by a simultaneous diminution of sensory and motor conduction, the former is usually depressed in a much greater measure. Sensation, therefore, may be destroyed, while the motor impulses are still able to pass through the block. The return of conduction following the removal of the pressure is usually associated with a peculiar pricking sensation in the region supplied by this nerve. While no adequate explanation of this phenomenon can be given, it is commonly assigned to processes of excitation, *i.e.*, to a temporary increase in the irritability of the nerve tissue so affected. In fact, it has been stated by Weber, Schiff, and others that an increased excitability of the nerve is also experienced directly after its division. Compression-paralysis is usually ushered in by a hyperactivity of the distant muscles. It seems, however, that the development of this initial heightened irritability depends upon the character of the injury as well as upon the quickness with which it is effected.

Mechanical influences are prone to give rise to an initial phase of excitation unless permitted to act gradually,¹ while chemical agents and cold do not. The degree of pressure which may be brought to bear before conduction is abolished, has been determined by Ducceschi² and Bethe.³ The former employed a thin silk thread which was drawn around the nerve and slightly weighted at one end. A weight of a few grams sufficed to diminish the conduction, while a reduction of the diameter of the nerve to one-third or one-fourth of normal abolished it altogether. Naturally, a compression of this intensity affects the enveloping sheaths and perifibrillar substance

In this category belong the paralyses in the domain of the recurrent nerve following aneurisms of the branches of the aorta, and the paralysis of the arm muscles in consequence of the pressure of crutches.

² Pflüger's Archiv, lxxxiii, 1901, 38.

³ Allg. Anat. und Physiol. des Nervensystemes, Leipzig, 1903.

long before it actually causes an interruption of the fibrillæ of the axis-cylinders.

The fact that temperature influences the speed of conduction has already been established by the early experiments of Helmholtz. The relationship between these two factors is a direct one, *i.e.*, the higher the temperature, the more rapid the conduction, but this rule is applicable only within physiological limits. In the case of the motor nerves of man, variations between 30 and 90 m. per second have been obtained. This is also true of the nerves of invertebrates, those innervating the claws of the lobster, showing a velocity of 6 m. at 10° C., and of 12 m. at 20° C. The motor fibers of the sciatic nerve of the frog cease to conduct at 41–44° C., but may recover if the temperature is again lowered. At 50° C. their conductivity is lost altogether. It is also of some interest to note that the velocity of the nerve impulse follows the van't Hoff law for chemical reactions, because, as has been shown by Snyder,¹ a rise in temperature of 10° C. approximately doubles the conduction. This fact may be employed as a proof that conduction by nerve entails certain chemical changes, because most physical processes present for this range of temperature a relationship of only 1:1 or a relationship barely above unity.

Unusual changes in temperature, and especially those beyond physiological limits, cannot be considered as constituting pure thermal influences, because they are prone to injure the nerve tissue by bringing about a loss of water or certain differences in its electrical tension. In this category belongs the abolition of conduction in consequence of cauterization and extreme cooling. Thus, the application of ice to the region of the ulnar nerve at the elbow results at first in sensations of pain and finally in a complete loss of sensations.

A nerve may be kept in a physiological condition by frequently moistening it with normal saline solution, but its complete immersion in this solution (0.6 per cent.) is generally followed by phenomena of excitation which, however, do not appear if Locke's or Ringer's solution is employed instead. Overton² has shown that nerve-muscle preparations retain their functional qualities in the latter even after 15 to 20 days. Immersion in water diminishes the irritability of nerve. Moreover, it is a matter of common observation that its drying leads to violent contractions of the muscle which, to begin with, are clonic in character but soon become tetanic. Acids do not irritate unless concentrated;³ alkalies, on the other hand, stimulate even in solutions of 0.8–1.0 per cent. According to Mathews,⁴ the different solutions of the sodium salts act as exciting agents only in high concentrations, but some of them also stimulate when isotonic

¹ Am. Jour. of Physiol., xxii, 1908, 179; also see: Ranitz, Pflüger's Archiv, lxxviii, 1907, 601.

² Pflüger's Archiv, cv, 1904, 256.

³ Kühne, Archiv für Anat. und Physiol., 1860, 315.

⁴ Am. Jour. of Physiol., xi, 1904, 455.

to nerve tissue. Potassium salts depress. The same is true of magnesium sulphate. Conduction may be temporarily blocked by means of this salt and as effectively as by the application of ice or certain narcotics. As a general anesthetic this salt is useless and dangerous.¹

The most important agents influencing the activity of nerve-tissue belong to the group of the anesthetics. Ether and chloroform diminish the irritability and conductivity, the latter agent being a more powerful depressant than the former. In these cases, the conductivity usually persists for sometime after the excitability has been thoroughly abolished. Alcohol diminishes the conductivity, but does not materially affect the irritability. Carbon dioxid diminishes the excitability and finally also the conductivity. Among the narcotics opium, cocain, curarin and chloral hydrate act as depressants. The conductivity of nerve may also be gradually destroyed by depriving it of oxygen. This matter will be more fully discussed later on. Lastly, the irritability and conductivity of nerve may also be varied by the galvanic current. As this effect is of fundamental importance in formulating "Pflüger's Law" and the "Law of Unipolar Stimulation" of normal muscle and nerve, it will be more fully discussed later on.

The Nature of Conduction.—In spite of the many views which have been formulated in explanation of the cause of conduction by nerve, it cannot be said at this time that the exact nature of this process has been fully established. Thus, it has been suggested that a nerve-fiber is a tube containing a liquid or luminiferous ether, which either flows from place to place or oscillates back and forth. Others, again, have compared the nerve-fiber to a metal wire and the wave of excitation to a progressive charge of electricity. Still others have stated that the excitation arises in consequence of an explosive chemical change which then advances along the nerve-fiber. Without entering into a detailed discussion of these different views, it may be said that they are based upon two fundamental conceptions, attaching to conduction either a purely *physical* or a purely *chemical* nature.

The adherents of the former theory claim that the wave of excitation or nerve impulse is a physical force propagated along nerve-fibers without the latter undergoing metabolic changes. It has been suggested, on the one hand, that it consists of a delicate quivering of the molecular constituents of the nerve, and, on the other, that it is due to a definite shear along the colloidal substance of the axis-cylinder. An analogous process is the conduction of electricity along copper wires which necessitates no consumption of material. In accordance with this theory, the nerve impulse consists solely of an electrical wave which is known to pass along a nerve whenever it is activated.

This entire process may be illustrated very convincingly with the help of the so-called core-conductor, described by Hermann.² A thin platinum wire is enclosed in a glass tube filled with a solution of zinc sulphate. In the several pairs

¹ Meltzer and Peck, Jour. of the Am. Med. Assoc., lxxvii, 1916, 1131.

² Pflüger's Archiv, v, 1872, 264; also see: Matteucci, Compt. rend., lvi, 1863, 760.

of collaterals are placed zinc electrodes which in turn are connected with the wires leading to a corresponding number of galvanometers. Thus, the central wire is made to represent the axis-cylinder, and the surrounding zinc solution the less conductile myelin sheath, but it may also be said that the former corresponds to one of the fibrilla comprising the axis-cylinder and the latter to the perifibrillar substance investing it. If the end of this conductor is now stimulated with induction shocks, the galvanometers along its course will indicate the passage of an electrical wave in a direction away from the point of stimulation. This model also gives rise to electrotonic alterations similar to those encountered in normal nerve.

In accordance with the second theory, which assumes that the nerve impulse consists in progressive chemical changes, it is held that conduction necessitates the destruction of some of the constituents of the nerve. If gun powder is spread out upon a flat surface in the form of a narrow band and a spark is applied to it at one end, an explosive chemical reaction ensues during which this material is progressively consumed. Very obviously, conduction in nerve is not associated with changes of this intensity, but it can no longer be doubted that nerve tissue undergoes certain metabolic alterations in consequence of its

FIG. 77.—SCHEMA TO SHOW THE ACTION OF THE CORE-MODEL.

p, The polarizing current; *g'* and *g*, the galvanometers showing the anelectrotonic and catelectrotonic currents, respectively. (Howell.)

activity which differ from those of other tissues only in a quantitative way. This point will be proved with absolute certainty by the succeeding discussion. Consequently, a nerve impulse may be regarded primarily as a wave of chemical change which is accompanied by a liberation of chemical energy. In addition, the ensuing electrolytic dissociation also permits of the generation of electrical energy. Under ordinary conditions, the latter is the only means at our disposal to recognize the nerve impulse as it sweeps over a nerve. But while this phenomenon may be proved to possess a distinct chemico-physical basis, its true character has not been established as yet. For the present it must suffice to characterize it as a chemico-physical disturbance, the most evident product of which is an electrical change, commonly called the wave of negativity.

The Liberation of Energy by Nerve.—In accordance with the preceding statement it must be evident that we cannot ascribe a chemico-physical basis to the nerve impulse unless it can be shown that it is actually accompanied by chemical changes such as ordinarily serve as indications of metabolism and fatigue. We have previously seen that the contraction of muscle is associated with a liberation of

mechanical energy, heat and electricity, but inasmuch as nerve serves merely as an instrument of conduction, it cannot be expected to give rise to considerable amounts of energy. It is a well-known fact that there is no mechanical change in the active nerve and hence, the only point for us to determine is whether it presents any indications of the evolution of heat or electricity. So far it has not been possible to demonstrate the occurrence of thermic changes with any degree of certainty. Rolleston,¹ for example, employed a delicate bolometer indicating differences in temperature of $\frac{1}{5000}^{\circ}\text{C.}$, but no increase in temperature could be detected. Negative results have also been obtained by A. V. Hill² who made use of very sensitive thermoelectric elements, indicating changes of a hundred millionth of a degree. Cremer,³ on the other hand, does not deny the possibility of thermogenesis, but states that the heat liberated by active nerve is less than the Joule's heat of the stimulating current. Garten,⁴ moreover, be-

FIG. 78.—CURRENT OF INJURY IN NERVE.

The cross-section of the nerve is galvanometrically negative to its longitudinal surface.

lieves it possible that the nerve possesses the power of quickly absorbing the slight amount of heat developed in the course of its metabolism. In the face of more recent observations, it can scarcely be denied that nerve undergoes metabolic changes, and hence, in analogy with other tissues, it may be inferred that nerve also liberates at least a slight amount of heat.

In contrast to these rather indefinite results, it has been fully established that nerve liberates electrical energy. Thus, if the poles of a galvanometer are connected with two separate regions of an uninjured nerve, the needle remains perfectly stationary, proving thereby that a normal nerve at rest is isoelectric or equipotential. But if one of the non-polarizable electrodes is now adjusted to the cross-section of this nerve, a deflection of the needle results at once (Fig. 78), indicating thereby the existence of a demarcation current which we call the *current of injury*.⁵ While its strength equals only 0.02 volt

¹ Jour. of Physiol., xi, 1890, 208.

² Ibid., xliii, 1912, 433.

³ Münchener med. Wochenschr., 1895.

⁴ Physiol. der markl. Nerven, Jena, 1903.

⁵ Discovered by DuBois-Reymond in 1846 (Arch. für Anat. u. Physiol., 1867, 417).

in medullated nerves, it is said to be more intense in non-medullated nerves. Moreover, its strength diminishes very rapidly and especially in the nerves of warm-blooded animals, but the previous difference in potential may again be established by making a new section next to the first. Injured nerves, therefore, behave in the same manner as injured or degenerating muscle. In either tissue the current flows

FIG. 79.—CURRENT OF ACTION IN NERVE.

To begin with the nerve shows the current of injury indicated by the arrows (as in Fig. 78). When stimulated at *S* a negativity passes along the nerve which, on reaching Pole *A*, causes a partial reversal of the current of injury, indicated by the needle.

through the galvanometer from the non-injured to the injured portion, and inside the nerve from the injured to the non-injured. The latter we call the *axial current*. An interesting modification of this axial current¹ has been observed in nerves normally possessing a mixed direction of conduction. Thus, it has been found that the two cross-sections of a nerve are equipotential only in a mixed nerve, while

FIG. 80.—Schema to indicate the procedure used to prove the diphasic character of the action current. The isoelectric condition obtained to begin with is destroyed as soon as the wave of negativity arrives at lead *A*.

nerves composed either of afferent or efferent fibers, present distinct differences in potential. In an afferent nerve, the central cross-section is galvanometrically negative to the peripheral, while in an efferent one it is positive to the peripheral. Thus, excised segments of nerve always exhibit an axial stream in a direction opposite to that of their normal conduction, namely, descending in afferent nerves and ascending in efferent nerves.

¹ DuBois-Reymond, *Unters. über tier. Elektrizität*, ii, 252; also see: Weiss, *Pföger's Archiv*, cviii, 1905, 416.

When stimulated and made to conduct, nerve tissue invariably exhibits a *current of action*, the region of the impulse being galvanometrically negative to the resting portion of the nerve. This may be proved by first deviating the needle of the galvanometer by a current of injury (Fig. 79) and then stimulating its distant end with an induction shock (*S*). As the wave of negativity reaches the plus pole (*A*) of the current of injury, it reduces its potential and causes a partial reversal of the current of injury. The needle of the galvanometer then swings toward and beyond zero. Immediately, thereafter, the needle assumes its former position, namely at a time when the wave of negativity has arrived at the negative injured cross-section of the nerve (*B*). Consequently, the current of action in nerve is diphasic.

The diphasic character of the action current may be shown most advantageously by placing both leads of the galvanometer upon the longitudinal surface of the nerve (Fig. 80). This system is isoelectric, because both uninjured points *A* and *B* have the same potential. If the nerve is now excited at *S* with a single induction shock, the wave of negativity resulting therefrom, will cause a deflection of the needle when it reaches *A*, because *B* is still positive. A moment, thereafter, a reversal will take place, *B* now being negative and *A* positive.

In harmony with the results obtained with the help of the rheoscopic frog preparation, the action current of nerve may also be employed as a stimulus for a neighboring nerve. If a short segment of a nerve (*A*) is placed next to the nerve of a nerve-muscle preparation (*B*), the stimulation of *A* invariably gives rise to a contraction of the muscle. In explanation of this phenomenon it must be mentioned that the contraction of muscle *B* is effected in an indirect manner, *i.e.*, the stimulation of nerve *A* gives rise to an action current which serves as a stimulus for nerve *B*. The impulse set up in nerve *B* then descends to the muscle and causes it to contract. It is to be noted, therefore, that the impulse in nerve *B* is not continuous with the first, but is developed in a manner similar to that of an induced current in the secondary coil of an inductorium. The impulse (action current) traversing nerve *A*, induces an impulse in nerve *B*.

Action currents may also be detected in peripheral nerves if the corresponding area of the cerebral cortex is stimulated. This result is also obtained if the corresponding anterior root of the spinal cord is used instead. Sensory nerves are to be preferred for experiments of this kind, because the stimulation by means of the electrical current may then be dispensed with. Thus, Kühne and Steiner¹ have detected negative variations in the optic nerve whenever the retina was exposed to light, while Steinach² has noted similar fluctuations in the sciatic nerve of the frog on stimulation of the tactile receptors of the foot. In the sensory nerves of the lateral organ of fishes these currents have been observed by Fuchs.³ Records

FIG. 81.—SCHEMA TO SHOW HOW A NERVE-MUSCLE PREPARATION (*B*) MAY BE STIMULATED BY AN ACTION CURRENT IN NERVE *A*.

¹ Untersuchungen aus dem physiol. Inst. zu Heidelberg, iv, 1881, 64.

² Pfüger's Archiv, lxiii, 1896, 495.

³ Ibid., lx, 1895, 173.

have also been taken of the negative variations in the depressor nerve on increasing the blood-pressure in the aorta¹ and of those occurring in the vagus nerve synchronously with the respiratory movements.²

The Relation of the Nerve Impulse to the Wave of Negativity and the Action Current.—The preceding discussion must have satisfactorily proven that the wave of negativity and the nerve impulse are practically synonymous phenomena, because they advance with the same velocity and cannot be dissociated by any known means.

A nerve impulse may be generated by mechanical, electrical, thermal, photic and chemical means, and may be the result of either direct or indirect (reflex) stimulation. If regarded as a purely physical phenomenon, it will be seen immediately that the impulse must consist solely of a wave of negativity, while if considered as a chemical phenomenon, it must be the product of certain chemical changes. In accordance with the second view, which is the more widely accepted at the present time, the nerve impulse consists of a progressive chemical process entailing catabolism and anabolism. One of the results of these changes is the wave of negativity which thus assumes the character of a true current of action. This relationship having been established, the negative wave is to be regarded as an associative phenomenon of the chemical changes. Hence, the phenomena of conduction in nerve are very similar to those taking place in muscle whenever a wave of contraction sweeps over its constituent fibers. The evidence favoring this chemico-physical explanation of the nerve impulse, is chiefly derived from the fact that the conduction in nerve entails certain metabolic changes, which will be more fully discussed in the succeeding paragraphs.

The Metabolism of Nerve During Activity.—In accordance with the observation that contracting muscle yields lactic acid, carbon dioxide and other fatigue substances, efforts have repeatedly been made to show that these bodies are also formed in active nerves. Inasmuch as the functional capacity of nerve varies directly with the carbon dioxide content of the air surrounding it, A. D. Waller³ assumed at an early date that this gas is actually liberated in the course of the activity of this tissue. It has recently been proved by Tashiro⁴ that this assumption is correct. By employing an extremely delicate indicator it could be shown that even the resting nerves of frogs produce a measurable quantity of carbon dioxide, and besides, it was found that this amount may be greatly increased by stimulation. Positive evidence of nerve metabolism has also been furnished by Bayer⁵ and Fröhlich,⁶ because these investigators have shown that oxygen is abso-

¹ Tschermak, Pflüger's Archiv, xciii, 1903, 24.

² Lewandowsky, Pflüger's Archiv, lxxiii, 1898, 298; also see: Einthoven, Quart. Jour. of Exp. Physiol., i, 1908, 243.

³ Brain, lxxvi, 1897, 569, and Proc. R. Soc., London, lxii, 1897, 80.

⁴ Am. Jour. of Physiol., xxxii, 1913, 137.

⁵ Zeitschr. für allg. physiol., ii, 1903, 169.

⁶ Ibid., iii, 1904, 131.

lutely necessary for the proper function of this tissue. These experiments consisted essentially in enclosing the nerve of a nerve-muscle preparation in a small glass receptacle so that it could easily be subjected to the influence of an inert gas, such as hydrogen or nitrogen (Fig. 82). While the effect was never very striking, it could nevertheless be shown that the irritability and conductivity of the nerve (*N*) decreased very markedly if kept in this inert medium for a period of several hours. Moreover, the subsequent displacement of the inert gas by oxygen was followed within a few minutes by a complete restoration of the function of the nerve. This proves that oxygen is one of the prerequisites of nerve metabolism. As far as the production of acid is concerned, no positive results have been obtained. In this regard nerves differ very materially from the gray matter of the central nervous system, because the latter has been shown to become decidedly acid as a result of activity.¹

The fact that nerve tissue undergoes assimilative and dissimilative changes, is also betrayed by the high value of the temperature coefficient of conduction. It has previously been mentioned that the speed of the nerve-impulse is greatest in warm-blooded animals and that even moderate rises in temperature give rise to a much greater rapidity of conduction. In this regard nerve-tissue behaves in accordance with the van't Hoff law for chemical reactions. In addition, it should be mentioned that nerve possesses a very appreciable refractory period during which it cannot respond to stimuli. In the case of the sciatic nerve of the frog this period amounts to 0.002 second, but may be increased by cold, asphyxia, anesthetics and narcotics. It appears, therefore, that nerve-tissue requires a certain time for its anabolic changes and hence, if a second stimulus is brought to bear upon it before it has had sufficient time to complete these processes, it must necessarily fail to conduct the succeeding impulse.

The brevity of the refractory period of nerve suggests that its power of assimilation is unusually great, but this is rather to be expected, because the conduction in nerve does not require a considerable expenditure of energy so that the compensation for the preceding dissimilation can easily be effected without profound chemical changes. This deduction is in complete harmony with the structural peculiarities of nerve. Contrary to the gray matter of the central nervous system, the white matter, as well as the peripheral nerves, possesses a scanty and ill-defined network of blood capillaries and lymph channels. This implies that the blood supply of this

FIG. 82.—
FATIGUE OF
NERVE.

N, nerve of
nerve muscle
preparation
drawn through
glass chamber.
The latter is
connected with Kipp
apparatus *C*.
The stimulus is
applied at *S*.

¹ Funke, Arch. für Anat. und Physiol., 1859, 835.

tissue is inconsiderable. Contrariwise, however, it is evident that its storative qualities are excellent, because while the interruption of its blood supply eventually leads to a reduction of its irritability and conductivity, this depression is not quickly forthcoming; in fact, the nerves of the cold-blooded animals may retain these properties for a surprisingly long period of time after their excision.

Fatigue of Nerve.—Nerve-tissue possesses certain qualities which fortify it against excessive dissimulation and thus prevent it from entering the state of fatigue with the same readiness as other tissues. The earlier experiments pertaining to the development of fatigue in nerve, were made with nerve-muscle preparations. In all these instances the contraction of the gastrocnemius muscle served as the index of activity. It is a well-known fact that the repeated stimulation of any musculomotor nerve eventually leads to a cessation of the contractions, but this result has been proved to be due to a fatigue of the end-plates and not to an exhaustion of the nerve itself. Consequently, experiments of this kind cannot yield reliable results unless the muscle is protected in some way against these impulses, while the nerve is not. A block of this kind may be established quite easily with the aid of curare. To begin with, it must be shown that each stimulation of the nerve produces a contraction of the muscle. If a solution of curare is now applied to the latter, the ensuing paralysis of the motor plates prevents the impulses from reaching the effector¹ until the action of this drug has again weakened. During the interim, therefore, the nerve may be stimulated without producing a muscular reaction. By this means it has been found that nerves may be made to conduct impulses for many hours without becoming fatigued. Similar tests have been made with the vagus nerve, the inhibition of the heart being prevented during these repeated stimulations by the administration of atropin.² As soon as the action of this drug weakened after many hours, the stimulations again became effective. Very similar results have been obtained by stimulating the chorda tympani of the sub-maxillary gland after the administration of atropin. Secretion was resumed in this instance as soon as the action of this drug diminished sufficiently to permit the impulses to break through.³ It has also been shown that a galvanometer connected with a nerve indicates a wave of negativity with every excitation, and even if these stimulations are continued for many hours. Thus, Beck⁴ has stimulated the cervical sympathetic nerve during seventeen hours without succeeding in greatly lessening the dilatation of the pupil.

¹ Bernstein, Pfüger's Archiv, xv, 1877, 289; Wedenski, Zentralblatt der med. Wissensch., 1884, and Bowditch, Jour. of Physiol., vi, 1885, 133. The effect of curare may be removed within a few minutes by the salicylate of physostigmin. (Düreg, Zentralbl. für Physiol., xv, 1902, 75.)

² Scana, Arch. für Anat. u. Physiol., 1891, 315.

³ Lambert, Compt. rend., 1894, 511; also see: Mascheck, Sitzungsber. d. Wiener Akad., xcvi, 1887.

⁴ Pfüger's Archiv, cxxii, 1908, 585.

These results have led to the early belief that nerve-tissue cannot be fatigued and that the nerve impulse is a physical phenomenon. It should be remembered, however, that these deductions have been based upon experiments which were made in a medium of air and under conditions greatly favoring the activity of nerve. Contrary to the view just expressed, Bayer and Fröhlich have shown that the refractory period of nerve may be considerably lengthened by means of narcotics or by displacing the air by an inert gas, such as hydrogen or nitrogen. It was also noticed that the power of conduction of nerve is markedly diminished in a medium of this kind and remains so until the nerve has again been transferred into an atmosphere containing oxygen. Thörner¹ has modified this experiment by placing the nerves of two nerve-muscle preparations in a chamber containing nitrogen (Fig. 83). One of these nerves was then subjected to a tetanizing current centrally to this chamber (A). By measuring the amplitude of the wave of negativity it was found that the excitability and conductivity decreased very rapidly in the tetanized nerve, but a similar, although much slighter, effect was also detected in the inactive nerve (B). Further evidence in favor of the view that nerves may be fatigued, has more recently been presented by Garten.² While testing different non-medullated nerves, it was noted that the action currents sweeping over the olfactorius of the pike, ceased very shortly after the beginning of its tetanization and did not reappear even after the electrodes had been applied to some other part of this nerve. This fact tends to show that the fatigue of nerve is never restricted to the segment stimulated but involves this structure in its entirety. Very similar results have been obtained by Burian³ in the non-medullated nerves of cephalopods. This investigator, moreover, has proved that these symptoms of fatigue are not dependent upon electrotonic alterations in the area stimulated. In summing up, it may be stated that the difficulties formerly encountered in proving fatigue in nerve must be assigned

FIG. 83.—FATIGUE OF NERVE.

A and B two nerves placed in glass chamber. The latter is connected through C with gas generator. S points of stimulation; S, galvanometers placed upon nerves to test their irritability.

¹ Zeitschr. für allg. Physiol., viii, 1908, 530.

² Beiträge zur Physiol. der markl. Nerven, Jena, 1903; also see: Snowton, Proc. Soc., lxvi, 1900, 379.

³ Intern. Kongress der Physiol., Heidelberg, 1907.

very largely to the low intensity of the metabolism of this tissue as well as to its remarkable affinity for oxygen. Nerve-tissue is capable of assimilating this gas in the briefest possible time from almost any source. In this regard nerve differs materially from the cell-bodies of the neurons, because the latter display a very intense metabolism and may therefore be more easily fatigued.

CHAPTER XIII

THE REACTION OF NORMAL AND ABNORMAL NERVE AND MUSCLE TO THE CONSTANT AND INTERRUPTED ELECTRICAL CURRENTS

Electrotonus.—The subsequent discussion should prove of particular value, because the facts now to be dealt with are absolutely essential for a thorough understanding of the behavior of human nerve and muscle when affected by degenerative changes. If we confine ourselves for the present to the constant or galvanic current, it is to be noted that the nerve must first be connected with the battery by means of two non-polarizable electrodes which are placed at a moderate dis-

FIG. 84.—SCHEMATA TO SHOW THE ARRANGEMENT USED FOR THE STIMULATION WITH THE DESCENDING OR ASCENDING CURRENT.

D, descending; A, ascending.

tance from one another. The electrode joined with the positive pole of the generator then serves as the point of entrance of the current into the nerve, and the one united with the negative pole, as its point of exit. The former constitutes the anode (+) and the latter the cathode (-). Provision must also be made to be able to change the potential of these electrodes at will. This end is attained by means of a pole changer. In this way, the anode may be placed either near to or far away from the central end of the nerve (Fig. 84). If the former, the current must sweep over the nerve in a direction from center to periphery. It is then known as a *descending current*. If the

latter adjustment is used, the current must pass from the periphery toward the center. It is then called an *ascending current*.

In the second place, attention should be called to the fact that the passage of a constant current through a nerve gives rise to certain chemico-physical changes in the regions of the anode and cathode which have been designated by DuBois-Reymond as *electrotonus* (1843). This condition manifests itself in profound alterations in the irritability and conductivity of the nerve. This change constitutes *physiological electrotonus*, the one occurring in the region of the anode being known as *anelectrotonus* and the one at the cathode as *catelectrotonus*. The physiological electrotonus finds its origin in the so-called electrotonic currents which arise in consequence of electrolysis and polarization. The latter may be designated as *physical electrotonus*.

Nerve is a moist conductor and hence, it need not surprise us to find that the passage of the galvanic current induces certain processes of electrolysis and dissociation which attain their maximal intensity at the electrodes, *i.e.*, at the points of entrance and exit of the current. Inasmuch as the acid negative ions of the electrolytes are transferred to the anode, this region must assume an acid reaction, while the accumulation of the basic positive ions upon the cathode must render the latter alkaline. In the course of time, this accumulation of negative ions upon the anode and of positive ions upon the cathode gives rise to the so-called *polarization current*, *i.e.*, to an electrical interchange, the direction of which is opposite to that of the original polarizing current.

This polarization becomes most intense if metal electrodes are employed, but the aforesaid changes then appear to be confined to the points of contact between the metal and the nerve. If non-polarizable electrodes are used, this *external* form of polarization gives way to the *internal* form. Although still most conspicuous at the anode and cathode, these changes are then less closely restricted to the surfaces of the electrodes and spread with steadily decreasing density into the region between these two poles as well as into those situated immediately outside of them. The distance to which they extend outside the poles depends upon the strength of the primary galvanic current. Thus, electrotonus may be said to be *intrapolar* and *extrapolar*¹ in its character.

In this connection emphasis should be placed upon the fact that these electrotonic currents are absolutely distinct from the nerve impulse, as well as from the wave of negativity or action current and the current of injury. Thus, it has been proven that their velocity is much greater than that of the nerve impulse as betrayed by the speed of the negative variation.² In the second place, it has been shown that they may attain a strength twenty-five times greater than that of the current of injury. Their distinctiveness is also indicated by the fact that

¹ Pflüger, Unters. über die Physiol. des Elektrotonus, Berlin, 1859.

² Gildermeister and Weis, Pflüger's Archiv, xciv, 1903, 509.

they persist during the entire period during which the galvanic current is passed through the nerve and that their direction may be altered repeatedly by simply reversing the primary current. Action currents, on the other hand, always retain the same direction and are of momentary duration. They may also be produced by mechanical, thermal and chemical stimuli, while the electrotonic currents cannot be generated by these means. Another means of differentiation is furnished by the fact that the polarization currents are strongest in the extrapolar regions and that their intensity diminishes with their distance from the poles. These statements imply that the passage of a galvanic current through nerve (polarizing current) gives rise first of all to electrotonic currents (polarization current) which in turn lead to the production of a nerve impulse. The latter, therefore, is the result of the first two conditions and is by no means a part of them.

Electrotonic Differences on the Making and Breaking of the Galvanic Current.—If the nerve of a nerve-muscle preparation is stimulated at definite intervals with a constant current of moderate strength, it will be found that the muscle reacts only on the making and on the breaking of this current, but not during the interim, in spite of the fact that the current continues to traverse the nerve. In accordance with DuBois-Reymond, it may therefore be stated that the stimulating agent is not the absolute strength of the current, but rather the abrupt change in its intensity which it suffers when it is made or broken. In other words, a stimulus invariably fails to stimulate as long as it remains constant, but becomes effective immediately if its striking force is suddenly altered. Secondly, it has been shown by Pflüger that the making of the galvanic current gives rise to electrotonic changes at the two poles, and that those at the anode are very different from those at the cathode. The same holds true of the breaking of the current, but naturally, the changes then occurring, cannot justly be classified as true anelectrotonic and catelectrotonic phenomena, because they do not arise during the passage of the current, but immediately after its cessation. Strictly speaking, therefore, they should be characterized as post-anelectrotonic and post-catelectrotonic.

These differences in the functional condition of the nerve at the points of entrance and exit of the constant current may be briefly summarized as follows:

(a) On the making of the current the excitability of the nerve is markedly increased at the cathode and decreased at the anode. These changes are most pronounced at the poles, but also spread with gradually decreasing intensity into the intrapolar and extrapolar regions. Consequently, an indifferent zone must exist somewhere between these two poles, namely at the junction between the area of heightened cathodal excitability and the area of lessened anodal irritability.

(b) On the break of the current this condition is reversed, *i.e.*, the anodal region then possesses the greater irritability while the cathodal region is depressed. As has been stated above, this effect appears in reality after the breaking of the current, and forms therefore an electrotonic wave in the wake of the galvanic current. Thus, if the terminology of post-anelectrotonus and post-catelectrotonus is adhered

to, the term anelectrotonus signifies a depression and the term catelectrotonus an excitation occurring during the passage of the constant current.

(c) It is also essential to remember that the excitatory process developed at the cathode is always stronger than that developed at the anode.

It appears, therefore, that the wave of excitation constituting the nerve impulse, is developed at the cathode on the make and at the anode on the break of the current. This inference may be substantiated with a nerve-muscle preparation by simply recording making and breaking contractions when the anode is placed far away from the muscle and the cathode near to it. It will then be noted that the latent period of the making twitch is much shorter than that of the breaking twitch. This must necessarily be so, because in the former instance the nerve impulse arises at the cathode which is situated in the immediate vicinity of the muscle; while in the latter case it is produced at the anode which lies at some distance away from it. If

FIG. 85.—METHODS USED TO SHOW ELECTROTONIC CHANGES ON MAKING AND BREAKING OF GALVANIC CURRENT.

K, key for making and breaking of current; *P*, pole changer for making either end of muscle (*M*) anodic or cathodic; *D*, clamp applied to muscle to destroy contraction wave but not wave of excitation; *W*, weights attached to ends of muscle. These may be displaced by writing levers.

the current is now reversed so that the anode comes to lie near the muscle and the cathode far away from it, the latent period will show a greater length on the making of the current. On the making, the cathode serves as the stimulus and this pole is situated in this case far away from the muscle, while, on breaking, the excitation results at the anode which lies very near the muscle.

The preceding statement may also be proved by the procedure of Engelmann (Fig. 85). The positive and negative poles of a battery are connected with the two ends of a long muscle, such as the sartorius (*M*). This muscle is then constricted about midpoint between its poles by means of a clamp (*D*), the compression being just sufficient to prevent the contraction of one-half from being imparted to the other half without actually hindering the passage of the wave of

excitation. The writing levers (*W*), attached to the two ends of the muscle, are adjusted in the same ordinate, so that any difference in the onset of the contractions in the two halves will be indicated in the record. On making the current by closing the key (*k*), the contraction invariably begins at that end of the muscle which is connected with the cathode (*C*), while on breaking the current the end joined with the anode (*A*) is activated first. The polarity of the muscle is then changed by reversing the bridge of the Pohl commutator (*P*) interposed in the circuit, so that the previously cathodic end now becomes anodic. Although reversed as far as the muscle is concerned, the results will be identical with the preceding. This experiment may be modified in the following manner. It is a well-known fact that

FIG. 86.—METHOD OF TESTING THE ELECTROTONIC CONDITION OF NERVE.

K, key for making and breaking of constant current; *P*, pole changer for reversing current so that either pole may be made anodic or cathodic; *S*, point of stimulation of nerve by means of induction shocks; *W*, writing lever attached to muscle.

a much more lasting character may be imparted to the contractions by the use of a strong galvanic current. The one obtained on making the current is designated as Wendt's tetanus and the one on opening, as Ritter's tetanus. Engelmann has proved that these tetanic contractions remain confined to that end of the muscle in which they originate, namely, the making tetanus to the cathodic and the opening tetanus to the anodic end.

The phenomenon of electrotonus may also be reproduced with the help of the simple core-model described in one of the preceding paragraphs, but naturally, the conditions here met with are purely physical in their nature and are not complicated by physiological changes, as they are in living nerve. Thus, it has been noted that an electrolytic dissociation takes place between the metal core and the surrounding solution whenever a current is passed through it. The cathodic ions are made to move toward the anode and the anodic toward the cathode until true electrotonic currents have been produced.

Pfänger's Law of Contraction.—In order to show that the passage of a galvanic current gives rise to a cathodic area of excitation and an anodic area of depression, these regions may be stimulated at brief intervals either mechanically or by means of single induction shocks (Fig. 86). In the latter case, the electrodes (*S*), connected with

the secondary coil of an inductorium, are placed in the immediate vicinity of either the positive or negative non-polarizable electrode. By using a strength of induction which, when brought to bear upon the cathodic region, just barely produces a contraction of the muscle, it can easily be shown that this same stimulus applied to the anodic region, fails to incite a reaction. But even if the same minimal stimulus is employed for both regions, a comparison of the amplitude of the contractions then resulting will show immediately that the one obtained by stimulating at the cathode, is the larger of the two. In

this connection reference should also be made to the work of Bethe¹ who has shown that the anodic and cathodic regions possess different staining qualities. At the anode, the neurofibrils of the axis-cylinder lose their power of absorbing methylene-blue, while those situated at the cathode, show an abnormally high affinity for this dye.

The relative amplitudes of the contractions obtained by stimulating different points of the anodic and cathodic areas, have been made use of in the construction of a curve illustrating the manner in which the excitability of nerve is changed during the passage of the galvanic current. The following schema of Pflüger² (Fig. 87) shows that the subthreshold anode and suprathreshold cathode lines

FIG. 87.—ELECTROTONIC ALTERATIONS OF IRRITABILITY CAUSED BY WEAK, MEDIUM, AND STRONG BATTERY CURRENTS.

A and B indicate the points of application of the electrodes to the nerve, A being the anode, B the cathode. The horizontal line represents the nerve at normal irritability; the curved lines illustrate how the irritability is altered at different parts of the nerve with currents of different strengths. Curve y^1 shows the effect of a weak current, the part below the line indicating decreased, and that above the line increased irritability, at x^1 the curve crosses the line, this being the indifferent point at which the catelectrotonic effects are compensated for by anelectrotonic effects; y^2 gives the effect of a stronger current, and y^3 , of a still stronger current. As the strength of the current is increased the effect becomes greater and extends farther into the extrapolar regions. In the intrapolar region the indifferent point is seen to advance with increasing strengths of current from the anode toward the cathode. (*American Text-book of Physiology.*)

must vary in their position with the irritability of the nerve experimented upon and the strength of the constant (polarizing) current. This implies first of all that the polarization, or rather, the effect of the polarizing current must increase with the irritability of the nerve, and secondly, that the length of nerve so affected must increase with the strength of the current. At the point of confluency of these anodic and cathodic fields in the intrapolar region, a conflict arises in consequence of which the irritability remains unchanged. With a weak polarizing current, this indifferent point lies near the anode, while with stronger currents it is shifted more and more toward the cathode. This fact implies that strong currents are more depressant than weak currents, and hence, a point will eventually be reached when the depression also involves the cathode. The making increase in excita-

¹ Allg. Anat. und Physiol. des Nervensystemes, Leipzig, 1903.

² Unters. über die Physiol. des Elektrotonus, Berlin, 1859.

bility at the cathode is then much diminished. Strong currents, therefore, cause a depression at both poles but the cathodic depression is always less than that developed at the anode. Werigo¹ expresses this fact by saying that the cathodic depression is initiated by a brief period of excitation. It is to be remembered, however, that Fig. 87 represents the conditions prevailing during the passage of the constant current, when the term anelectrotonus is synonymous with depression and the term catelectrotonus with excitation, and does not portray the conditions existing subsequent to the breaking of the current. The post-anelectrotonic and post-catelectrotonic effects are the reverse of those just described, *i.e.*, while strong currents cause a depression at both poles, the cathodic region is now more highly depressed. At this time, the stimulus is derived from the anodic excitation still remaining.

These electrotonic differences are responsible for the occurrence of the phenomenon known as "secondary tetanus of nerve." If a long piece of the sciatic nerve of a frog (*A*) is placed beside the nerve of a nerve-muscle preparation (*B*), as is indicated in Fig. 81, the excitation of the central end of nerve (*A*) with a constant current invariably results in a contraction of the muscle. By making and breaking the current more rapidly, the muscle may be thrown into a complete state of tetanus. In this case, it is the electrotonic current in nerve (*A*) which produces the nerve impulse in (*B*) and the subsequent muscular reaction. It will be remembered from the previous discussion that this result may also be obtained with the aid of an ordinary action current.

It has been found by Pflüger that the making and breaking of a *weak* galvanic current gives rise to a contraction only on the make. In this case, it is immaterial whether the anode be situated near to or far away from the muscle, *i.e.*, the results are the same whether the current be ascending or descending. With a *medium* current a contraction is produced on the make as well as on the break, and this holds true for the ascending as well as for the descending current. With a *strong* current, the results are more complex, because the ascending current gives a contraction only on the break, and the descending current only on the make. These effects have been formulated into what is known as Pflüger's Law of Contraction which may be summarized as follows:

Current	Ascending		Descending	
	Make	Break	Make	Break
Weak.....	C	—	C	—
Medium.....	C	C	C	C
Strong.....	—	C	C	—

¹ Werigo, Pflüger's Archiv, lxxxiv, 1901, 547.

Clearly, this law is applicable only to excised nerve and muscle when tested under experimental conditions, but its practical value will become apparent later on in connection with the stimulation of normal and degenerating human muscle and nerve. Its explanation will present no difficulties if the following three fundamental data are borne in mind, namely:

(a) When a nerve is stimulated with a galvanic current, an excitatory process is set up at the cathode on the making and at the anode on the breaking of the current.

(b) The excitatory condition developed at the cathode on the making, is stronger than the one generated at the anode on the breaking of the current.

(c) The passage of a galvanic current through a nerve entails a decrease in its power of conduction which, although discernible at both poles, is most strongly

FIG. 88.—DIAGRAM ILLUSTRATING PFLÜGER'S LAW.

Asc., ascending current; *Desc.*, descending current; *W*, *M*, *S*, weak, medium and strong current. The effective stimulus is indicated in each case by cross marks.

marked in the region of the anode. Immediately upon the breaking of the current, the anodic conductivity returns to near normal, while the cathodic conductivity is diminished. With strong currents this anodic depression on the making becomes so powerful that it actually blocks the nerve impulse and thus prevents it from reaching its destination. The same holds true of the cathodic depression resulting after the breaking of the strong constant current.

With a weak ascending or descending current, only the two making stimuli are effective, because in this case the excitation which gives rise to the nerve impulse is developed at the cathode (Fig. 88). The nerve impulse resulting therefrom, reaches the muscle, because the depression at the anode on the making of the ascending current is not sufficiently intense to block it. The same holds true of the making of the descending current, and besides, the stimulating cathode now lies next to the muscle, so that nothing can prevent the passage of

the impulse into the latter. The breaking contractions are absent, because both anodic stimulations are as yet too weak. As the strength of the current is increased to medium (*M*), the breaking contractions also appear, because even the anodic stimulations have now attained a strength sufficient to generate nerve impulses. The making contractions, however, continue to be larger than the breaking, because the cathodic stimuli are more powerful than the anodic. With medium currents no direct blocking effects are obtained, although the anodic-making and cathodic-breaking depressions are now more powerful than during the passage of weak currents.

With a strong ascending current (*S*), no reaction is obtained on the making, because the anode is situated next to the muscle. The nerve impulse generated at this time at the cathode cannot reach the end-organ, because the strongly depressed and non-conductile anodic region intervenes. On the break of this current, however, the impulse can reach the motor organ without hindrance, because the now stimulating anode is situated near the muscle and the depressed cathodic area far away from it. With a strong descending current a contraction is obtained only on the making, because the stimulating cathode is now situated near the muscle and the depressed anode far away from it. On the breaking of this current, however, the impulse developed in the anodal region cannot reach the muscle, because the non-conductile cathode is interposed between it and the end-organ.

The Law of Contraction of Normal Human Nerve and Muscle.—

Pflüger's Law as such cannot be applied to human muscle and nerve, because the conditions here met with are entirely different from those presented by excised muscle. Living human muscle is covered by skin, adipose tissue, fascia and connective-tissue envelopes, and the nerves are generally so deeply placed that they are not accessible to stimulation by means of two widely separated electrodes. For this reason, their excitation is usually effected with a single electrode adjusted as follows: The battery consists of about 25 to 30 cells which may be quickly joined in series so as to be able to increase the strength of the current with the least possible loss in time. In this circuit is inserted a pole changer by means of which the polarity of the electrodes may be reversed at any moment. One of the electrodes consists of a broad metal plate wrapped in a bolster of cotton. The latter is moistened with saline solution to reduce the resistance of the skin. The other electrode is pointed and is equipped with a key which may be closed and opened at will. If a current of a certain voltage is permitted to pass through two electrodes of this construction, it will be found that the excitation invariably arises at the pointed one, because the current attains here its greatest density and striking force. At the broad metal plate, on the other hand, it is able to scatter more widely through the tissues without actually acquiring a high stimulating intensity. For this reason, the former is designated as the stimulating and the latter as the indifferent electrode.

This procedure is commonly called the unipolar method of stimulation (Chaveau). To begin with, the indifferent electrode is firmly applied to some part of the body, while the stimulating electrode is brought in contact with the region overlying the nerve or muscle to be tested. The accompanying Fig. 89 may serve to illustrate the arrangement generally employed in stimulating the muscles of the arm. But practically every voluntary muscle in our body may be tested in the same way, although its excitation is usually effected through its motor nerve by applying the active electrode to the region in which its nerve becomes most superficial. The location of these different *motor points* may be determined with the help of Figs. 90 and 91.

FIG. 89.—SCHEMA TO SHOW THE UNIPOLAR METHOD OF STIMULATION IN MAN.

The anode, +, is represented as the stimulating pole, applied over the median nerve. The cathode, —, is the indifferent pole. (Howell.)

If the stimulating electrode is made anodic, it will be found that neither the making nor the breaking of a weak galvanic current gives rise to a contraction. If the active electrode is now made cathodic, a contraction will be obtained on the making of this current. This reaction is usually called the cathodic closing contraction (C.C.C.). On repeating this procedure with a current of medium strength, it will be noted that the anode also becomes effective, a contraction now resulting both on the making and breaking of this type of current. These contractions are designated respectively as the anodic closing (A.C.C.) and anodic opening contraction (A.O.C.). The cathodic closure con-

traction (C.C.C.) already obtained with the weak current, is, of course, retained, but no effect is as yet in evidence on the break with the cathode presenting. This cathodic opening contraction (C.O.C.) appears only after the strength of the current has been materially increased by the addition of several cells. Attention should also be called at this time to the fact that strong currents frequently give rise to contracture-like reactions, which are designated as *galvanotonus*. As far as human nerve and muscle are concerned, it will be seen, there-

FIG. 90.—MOTOR POINTS IN UPPER EXTREMITY. (Howell.)

fore, that the gradual increase of the constant current brings forth these contractions in the order indicated in the succeeding table:

Galvanic current		
Weak	Medium	Strong
C.C.C.	C.C.C.	C.C.C.
.....	A.C.C.	A.C.C.
.....	A.O.C.	A.O.C.
.....		C.O.C.

In the same manner as the results obtained with excised muscle and nerve, have been formulated into Pflüger's law of *polar stimulation*, so may the present results upon human muscle and nerve be combined into the law of *unipolar stimulation*. But inasmuch as these laws have a different experimental basis, they cannot really be compared with one another unless this comparison be restricted to the causes under-

FIG. 91.—NERVES AND MOTOR POINTS IN LOWER EXTREMITY. (Church and Peterson.)

lying them. A clear understanding of the second law requires first of all a brief recapitulation of the following three fundamental data:

(a) The making of a galvanic current gives rise to an excitation at the cathode, and its breaking to an excitation at the anode.

(b) The irritability developed at the cathode on the make of the current, is always greater than that generated at the anode on the break.

(c) The stimulating power of this current is greatest in its area of greatest density.

The effects of unipolar stimulation, however, are complicated by the fact that the electrodes cannot be applied directly to the nerve but only to the skin overlying, and hence, a number of peripolar regions invariably develop around the actual poles upon the nerve. If the stimulating electrode is anodic and the indifferent electrode cathodic, the various electrical lines enter the tissues as through a narrow gate and then spread out fan-like underneath, constantly seeking paths of least resistance. At the cathodic pole, these lines again converge and are finally combined into a number of smaller bundles. At every point where these lines enter the nerve there is established a secondary anode, and wherever they emerge, a secondary cathode. In this way, a number of secondary or physiological anodes and ca-

FIG. 92.—ROUGH SCHEMA OF ACTIVE THREADS OF CURRENT BY THE ORDINARY APPLICATION OF ELECTRODES TO THE SKIN OVER A NERVE (ULNAR NERVE).

The inactive threads are given in dotted lines (after Erb).

thodes are developed beneath the primary or physical anode as well as below the physical cathode. In brief, therefore, it may be stated that the results of the stimulation of human muscle and nerve are dependent upon the interaction of these physical and physiological poles.

A fuller explanation must take into account that the contraction, following the making of the current, is developed at the physiological cathode, while the one following the breaking of the current, is developed at the physiological anode. Now, since the stimulating electrode may be made either anodic or cathodic, and since physiological anodes and cathodes are developed in either case, four possibilities arise, namely:

(1) Anodic Stimulation:

- (a) On making we obtain the so-called anodic closing contraction in consequence of excitatory changes resulting at the physiological cathode beneath the physical anode.

- (b) On breaking we obtain the so-called anodic opening contraction which is due to the excitatory process at the physiological anode beneath the physical anode.
- (2) Cathodic Stimulation:
- (a) On making we obtain the so-called cathodic closure contraction in consequence of the excitation developed at the physiological cathode beneath the physical cathode.
- (b) On breaking we obtain the so-called cathodic opening contraction which is caused by the excitatory alterations at the physiological anode beneath the physical cathode.

It has been stated repeatedly that the cathodic irritability is stronger than the anodic. For this reason, the two making or closure contractions (C.C.C. and A.C.C.) must be stronger than the two break-

FIG. 93.—DIAGRAM SHOWING PHYSICAL AND PHYSIOLOGICAL ANODES AND CATHODES.

A, the physical anode, or positive electrode; K, the physical cathode, or negative electrode; a, a, a, physiological anodes; k, k, k, physiological cathodes. (*American Text-book of Physiology.*)

ing or opening contractions (A.O.C. and C.O.C). Thus, it only remains for us to see why the cathodic closure contraction precedes the anodic closure contraction and why the anodic opening contraction appears before the cathodic opening contraction. In brief, this sequence of the reactions is dependent upon differences in the density of the current. On making, the current acquires a greater density or striking force when the physiological cathode coincides with the physical cathode than when it lies in relation with the physical anode. In the first case, we obtain what might be termed a summation of effects between the inner physiological cathode and the outer physical cathode. The same explanation may be given for the fact that the anodic opening contraction develops before the cathodic opening contraction. The excitation on breaking being developed at the physiological anode, this stimulation becomes more effective if the physiological anode and physical anode coincide.

The Law of Contraction of Degenerated Human Nerve and Muscle.—When called upon to ascertain the functional condition of a certain muscle and its nerve, use should be made not only of the constant current but also of the induced current. It should be noted

first of all that degenerating muscle and nerve is very sensitive to the galvanic and relatively insensitive to the induced current, so that even a weak constant current may produce an exaggerated contraction, or galvanotonus, while strong induction shocks may fail entirely in eliciting a response. This fact in itself is suggestive of degeneration, because it indicates that the irritability of this particular muscle and nerve has become more nearly like that of all sluggishly reacting forms of protoplasm. A further means of differentiation is furnished by the so-called *law of degeneration* which is obtained by the same procedure as the law of unipolar stimulation, the stimulating electrode being applied either to the region of the muscle or to that of the nerve innervating it (Erb's reaction). For reasons not clearly understood, degenerated muscle reacts first on the making of the galvanic current when the anode is the active electrode, while, on breaking, the cathodic opening contraction is obtained before the anodic opening.¹ In advanced cases of degeneration, the galvanic excitability is also diminished, only the first contractions remaining in evidence until eventually even these disappear. The law of degeneration may be tabulated as follows:

Galvanic current		
Weak	Medium	Strong
A.C.C.	A.C.C.	A.C.C.
.....	C.C.C.	C.C.C.
.....	C.O.C.	C.O.C.
.....		A.O.C.

Chilarducci has suggested to place the stimulating electrode at some distance below the degenerated muscle, because a contraction may then be elicited with currents three or four times weaker than those ordinarily required for indirect excitation. Furthermore, contractions may then be evoked long after the direct stimulation has ceased to give positive effects. This phenomenon, which is called "reaction at a distance," may be used for the diagnosis of degeneration of long standing and unusual obscurity.

¹ Babinski, Compt. rend., 1899, 343.

PART II
THE BLOOD AND LYMPH
IMMUNITY
SECTION IV
THE BLOOD

CHAPTER XIV

GENERAL CHARACTERISTICS OF THE BLOOD

General Consideration.—The general body fluid of the lowest organisms possesses the simplest possible composition. It is widely distributed through the intercellular spaces and is separated from the surrounding medium by a very permeable membrane. Being thus fully exposed to osmotic influences from without, different nutritive substances are constantly forced into the organism, while its waste products are made to pass into the medium. These osmotic conditions, however, are adjusted in such a way that the general fluid of the body is quite unable to acquire a concentration much above that of the surrounding medium.

Separate circulatory channels are not present in the lower forms. Instead, the alimentary canal is called upon to perform a double function, namely, that of serving as a receptacle in which the nutritive substances undergo mechanical and chemical reductions, and that of distributing the assimilated material to the different parts of the body. A much higher stage of development is attained in those animals in which the alimentary tract assumes a variegated shape and in which its different recesses eventually become disconnected from the main channel to form the beginnings of the circulatory system. In this manner a number of internal reservoirs are developed, from the contents of which the tissue-cells derive their nourishment directly. But, while the body-fluid is thus more thoroughly protected against outside influences, its isolation is not complete, because it continues to be exposed, on the one hand, to the osmotic power of the contents of the alimentary canal and, on the other, to the conditions prevailing in the cells of the tissues.

With increasing cellular differentiation, this fluid of the celom gradually assumes the characteristics of real blood. Moreover, as the interior spaces become more variegated, certain elementary forces are

brought into play which cause the fluid to move in such a manner that delicate streams or even oscillatory currents are produced. The more efficient protection against outside influences, which is thus afforded the "blood," enables it to maintain a much greater complexity without materially hindering the osmotic interchanges.

In the higher animals, the blood assumes all the characteristics of a tissue, but in order that the cellular units of the body may be brought into relation with their nutritive source in the shortest possible time, it is made to move rapidly through a system of intricate and recurrent tubes, the driving force being furnished by a central muscular organ, the heart. Besides, these animals are equipped with a fluid known as the lymph¹ which serves the purpose of a medium

FIG. 94.—THE DEVELOPMENT OF THE CIRCULATORY SYSTEM.

Osmotic interchanges take place 1, between the medium and the substance of the cell through the cell wall; 2, between the contents of the alimentary canal (AC) and the tissue cells (B); 3, between the contents of the alimentary canal (AC) and its recesses, and the tissue cells (B and C), and 4, at the same two places after the recesses have become separated from the body canal.

for the osmotic interchanges between the blood and the tissues. Thus, as the amount of blood present in the body is relatively small whereas its complexity is great, it must be evident that the lymph forms an economic factor of greatest importance, because its copiousness and watery consistency enable it to enter the smallest spaces and to come in direct contact with practically every cell of the body. The cells, it is commonly stated, are bathed in lymph, while the blood itself does not actually touch them. This statement, however, is not intended to imply that these nutritive fluids are quite independent of one another. On the contrary, the lymph is derived originally from the blood in accordance with physico-chemical laws. It is diluted plasma which, however, is not lost to the blood, but is again returned

¹ A third circulating fluid is the chyle, but as this is merely lymph loaded with the products of digestion, it need not be considered separately. The same holds true of the intraocular fluid and of the liquor cerebrospinalis.

to it. Outside the capillary wall, the lymph serves as the medium with which the tissue cells interchange their material. This process having been completed, it then moves onward through the special channels constituting the lymphatic system, until it again reaches the venous collecting tubes of the main circulatory system. The lymph, so to speak, plays the part of a middle man between the blood and the cells.

The lymph is comparable to the general body-fluid of the lower animals, while the blood forms a much more specialized carrier. Functionally, however, these media must be regarded as fulfilling the same purpose, because they:

- (a) Equip the cells of the tissues with the material necessary for their existence, and remove from them the substances that are of no further use to them;
- (b) provide the tissues with oxygen in a readily assimilable form, and relieve them of carbon dioxide, one of the products of their metabolism;
- (c) help in the equalization and regulation of the body-temperature;
- (d) protect the organism against microbial infection and toxic influences of different kinds, and
- (e) disseminate the products of the ductless glands, known as atacoids.

The blood is a thick and viscous fluid, containing different bodies and substances in solution and suspension. It is composed of a fluid part, commonly designated as plasma, and a relatively large amount of solids. The latter embrace nutritive particles of all kinds, as well as formed elements, or corpuscles, which in turn are made up of red corpuscles or erythrocytes, white corpuscles or leukocytes, and blood platelets or thrombocytes.

Blood	{	Water.....	Plasma
		Nutritive particles, Blood dust (hemoconia)	
	{	Solids {	Corpuscles {
			red (erythrocytes)
			white (leukocytes)
			platelets (thrombocytes)

Relative Amount of Plasma and Corpuscles.—Two methods have been devised for the determination of the amount of the corpuscular material. The *direct method* possesses the advantage of being easily executed. The sample of blood to be examined is mixed with a definite quantity of potassium bichromate and is centrifugalized¹ until the corpuscular elements have been forced to the bottom of the receptacle. Since the glass-tubes used in this test are calibrated, the amounts of plasma and corpuscles may be read off directly. This entire procedure requires no special aptitude nor complicated apparatus and can be completed before coagulation has set in. It is also possible to ascertain the corpuscular content by measuring the electrical conductivity of the serum and corpuscles. This method depends upon the fact that the latter place a considerable resistance in the path of an electrical current which is directly proportional to the thickness of the

¹ For clinical purposes a small centrifuge, called a hematocrit, is commonly employed (Blix and Hedin).

layer formed by them. The *indirect method*, suggested by Hoppe-Seyler, is analytical in its nature and necessitates the following procedures. To begin with, the total amount of proteins in a definite quantity of defibrinated blood is determined and secondly, also the total protein content of the washed corpuscles contained in an equal amount of the same blood. It must be evident that the value obtained as a difference, corresponds to the amount of proteins contained in the serum of this sample of blood, and if the quantity of proteins in a special sample of the same blood is now ascertained, the proportion of serum in the blood as a whole can readily be calculated.

The proportion of plasma and corpuscles differs widely not only in animals of different species but also in animals of the same group. As a rule, the volume of the plasma is found to be much greater than that of the corpuscles, a relationship of 2:1 having been observed at times. The figures for human blood vary between 48 and 54 per cent., the average value for the corpuscles being about 50 per cent. by weight,¹ or 35 to 40 per cent. by volume. In the dog, the corpuscles constitute 36 per cent. and in the horse 34.5 per cent. by weight.

Color of the Blood.—When present in larger amounts, the blood exhibits a very characteristic color, varying between scarlet red and purple. Blood free from oxygen is dichroitic, dark red in reflected light and green in transmitted light. The color impression, actually derived from it, is in accord with the amounts of oxygen and carbon dioxid, or, more correctly speaking, with the amounts of oxyhemoglobin and reduced hemoglobin present therein.

The blood, or rather, the body-fluid, of the lower forms embraces pigments of different color. Red, violet, brown, green, and blue blood has been found. Furthermore, the pigment is not always held in the corpuscular elements, but may also occur free in suspension in the plasma. The earthworm, for example, possesses colorless corpuscles, while the blood-pigment, called hemerythrin, floats in the plasma. The red coloring material in the echinoderms is known as echinochrome, while the blue pigment of the molluscs and crustaceans is called hemocyanine, and the green pigment of worms, chlorocruorine.

The plasma itself is a clear, amber-colored liquid and does not impart a distinct color to the blood as a whole. Moreover, inasmuch as the leukocytes and platelets are colorless, the only constituents to which an influence of this kind may be attributed, are the red corpuscles. It should be emphasized, however, that single red cells give solely a sensation of very faint yellow, and that a distinct reddish color is obtained only when many of them are grouped together. The coloring matter of the red cells is the pigment of the hemoglobin.

On entering the lungs, the blood exhibits a dark red color, while that leaving them is much lighter. Obviously, therefore, its passage

¹ Arronet, Maly's Jahresber.; xvii; Schneider, Zentralblatt für Physiol., v, 1891, 362; and Stewart, Jour. of Physiol., xxiv, 1899, 356.

through the capillaries of this organ has enabled it to undergo a chemical change, which, as will become evident later, consists in an absorption of oxygen and a loss of carbon dioxid. As far as the coloring substance, hemoglobin, is concerned, its sojourn in the lungs has permitted it to acquire a certain amount of oxygen in place of that which has previously been turned over to the tissues. For this reason, the color of the blood may be employed as an index betraying the extent of the molecular union which has been effected between the hemoglobin and the oxygen of the respired air. In other words, it betrays the degree of aeration or oxygenation of the blood.

This explanation also accounts for the differences in the color of the blood in different parts of the vascular system. The most decided contrast is noted centrally in the large arteries and veins, while peripherally all intermediary shades between crimson and purple may be observed in accordance with the state of oxygenation of the blood in the region examined. In this connection mention should also be made of the fact that glandular and muscular activity is always associated with a greater flow of blood through the active organ, in consequence of which its venous discharge often assumes a color more like that of its arterial supply. Thus, it may be noted at times that the blood returned from the kidney, is much lighter than that of the inferior vena cava with which it eventually intermingles. A more copious supply of arterial blood is required by an organ or tissue when activated, because it needs more material for purposes of oxidation.

The appearance of the different exposed regions of the body, such as the lips, conjunctiva, nails, and mucous membrane of the mouth, is frequently employed as an index of the degree of aëration of the blood. Provided that the capacity of the blood-vessels of these parts has not been materially altered, a pink color signifies an adequate supply of oxygen, whereas a bluish hue suggests a poverty in oxygen and a superfluity in carbon dioxid. A dark blue color may readily be imparted to the circulating arterial blood by temporarily suspending the respiratory movements, or by permitting the animal to breathe air charged with carbon dioxid. Outside the body similar results may be obtained by removing the oxygen from the arterial blood by means of an air pump, or with the help of a reducing agent. During asphyxia the blood assumes an almost chocolate-brown color. This change can also be brought about locally by obstructing the venous return in a mechanical way. As the oxygen is gradually abstracted from the blood, the part experimented upon assumes a much darker appearance. Marked alterations also follow the administration of poisonous substances. Thus, carbon monoxid gives rise to a cherry-red color, while phenylhydrazin produces a dark-brown appearance. Quite similarly, venous blood may be made to assume a much lighter color by instituting vigorous respirations, or by shaking the shed blood in atmospheric air. Obviously, this change is brought about by an absorption of oxygen.

Even in thin layers blood is not transparent, because much of the light entering it is reflected from the surfaces of the formed elements. Its opacity, therefore, is caused chiefly by the red corpuscles.

Odor and Taste.—Blood possesses a salty taste and a faint odor. The latter is caused by volatile fatty acids held in solution, and becomes more distinct when concentrated sulphuric acid is added to the blood. While both factors vary somewhat even in animals of the same species, the odor of blood is usually sufficiently strong so that an animal, when wounded, may easily be followed by another possessing a keen sense of smell.

The Temperature.—The factor responsible for the temperature of the blood is the metabolism of the tissues. The heat given off by the cells is retained in full measure by the blood as long as it traverses well-protected channels, but is dissipated by it as soon as it reaches the more exposed parts of the body. Thus, it is found that the highest temperature prevails in the intrahepatic veins and the lowest in the blood-vessels of the fingers, nose and ears. Differences between 36° C. (97.7° F.) and 39.7° C. (103° F.) have been recorded; a fair average value for the blood in central channels is 38° C. (100° F.).

FIG. 95.—SMALL PYCNOMETER.

Specific Gravity.—This factor may be determined by means of a pycnometer. A small flask of glass, large enough to contain from 3 to 5 c.c. of blood, is weighed when empty and when filled with distilled water. The value so obtained is compared later on with the weight of this flask when filled with blood. It need scarcely be mentioned that the temperature must be the same for the two weighings. If the amount of blood is very small, short capillary tubes of glass may be employed, and, if large, flasks of a greater capacity than 5 c.c. The larger pycnometers are equipped with a thermometer as well as with an extra bulbular enlargement for the reception of that portion of the blood which is forced out when the flask is filled. A second method consists in permitting a drop of blood to fall into a fluid of known specific gravity. Various mixtures have been advocated for this purpose, for example, glycerin and water, or benzol and chloroform.¹ To begin with, the specific gravity should be adjusted at about 1.050. The procedure consists in quickly increasing or decreasing the specific gravity of this medium by the addition of a certain quantity of one or the other of these liquids, until the individual droplets of blood are held in the central mass of the mixture. At this moment their densities may be said to be practically the same. It is then only necessary to determine the specific gravity of the mixture by means of an ordinary hydrometer corrected to the mixture used. If a comparative study is made with different samples of blood, care must be taken to make the collections always from the same blood-vessel and under

¹ Hammerslag, *Zeitschr. für klin. Med.*, xx, 1892, 444.

as nearly identical conditions as possible, because, inasmuch as the internal friction of the blood varies with the size of the channel, its content in solids must necessarily be subject to fluctuations.

The specific gravity of the blood varies considerably. On the one hand, it is found that the general body-fluid of the lower forms possesses a density only slightly greater than that of water, and, on the other, that the blood of the higher animals represents a complex fluid of relatively high concentration. Obviously, therefore, the specific gravity must increase steadily, the highest values being present in the mammals. It is true, however, that the density of the blood of closely related animals is subject to only slight variations, so that a rather definite grouping of animals in accordance with this factor is made possible. Thus we find that the specific gravity of human blood exceeds that of the blood of the dog or cat, and that these in turn surpass that of the blood of the rabbit. The density of turtle's or frog's blood is much less than that of the mammalian blood. It must be emphasized, however, that individual variations do occur, as may be gathered from the fact that the specific gravity of human blood varies between 1.054 and 1.066. A fair average value is 1.060. In woman variations between 1.054 and 1.061 have been noted. Blood serum shows values ranging between 1.028 and 1.032. The red corpuscles possess a much greater density (1.090), a fact which accounts for the rather quick deposition of these bodies in blood to which an anticoagulating agent has been added.

It is also of interest to note that the specific gravity of the blood of the fetus is usually higher than that of the blood of the mother. Values, such as 1.066 for the former and 1.054 for the latter, are not unusual. During the first few days after birth rapid fluctuations between 1.060 and 1.080 are the rule, which, in all probability, are caused by a more copious production of tissue-fluid. During the first few months variations between 1.053 and 1.059 are encountered; a fair average value at this time being 1.056. A slightly higher figure, namely 1.058, is reached after the second and before the fourth year. Subsequent to the sixth year the average value is 1.061. This is retained throughout childhood.

Similar fluctuations have been recorded in dogs, cats, rabbits, and other animals. It may be stated, however, that the average value for dog's blood is somewhat lower (1.055) than that of the blood of man, but higher than that of the blood of the cat (1.050) or rabbit (1.045). On the whole, therefore, it is true that the specific gravity in a particular group of animals displays a certain constancy and that the minor variations just alluded to are dependent in a large measure upon such influences as age, sex, exercise, intake of solid food and water, as well as loss of water by perspiration and otherwise.¹

¹ The reader is reminded of the fact that very profound changes in the specific gravity are frequently encountered during pathological conditions. Very low values are noted in anemias, and very high values in diseases which are characterized by an increase in the number of the red blood cells (polycythemia).

Reaction.—The reaction of the blood as a whole, as well as that of the plasma, differs with the indicator. The earlier determinations, which have usually been made with glazed litmus paper, have given an alkaline reaction, while the more recent determinations, for which phenolphthalein has been employed, have shown that its reaction is acid. Its tendency in either direction, however, is so slight that it is really of very little importance.

Physicochemical researches have shown that the acidity or alkalinity of a fluid is dependent upon its content in hydrogen ions (+) and hydroxyl ions (−). This implies that acids are dissociated with a liberation of H ions, while bodies which give rise to OH ions, behave like alkalies. In illustration of this statement might be mentioned the dissociation of HCl into H (+) and Cl (−), and the dissociation of $NaOH$ into Na (+) and OH (−). Besides, the acidity or alkalinity of the aqueous solutions of these substances is directly proportional to the number of H ions or OH ions contained therein.

The number of OH ions contained in the blood and lymph has been determined by an electrical process¹ and has been found to be very small, and hence, as they do not exceed the H ions, the reaction cannot be decidedly alkaline, nor can it be acid for the same reason. The number of the H ions in the blood remains very constant, presumably on account of the presence in the plasma of the salts of carbonic acid, phosphoric acid and protein which are all very weak in their action. When acid is added to the blood, it reacts with the carbonates and phosphates. Carbonic acid and acid phosphates are produced which leave the body, in the first case, through the lungs and, in the second, through the kidneys. The tendency, therefore, is to establish a faint degree of alkalinity as quickly as possible.

Litmus paper gives a distinct alkaline reaction, because litmus acid which is the indicator in this particular case, unites with the Na of the $NaHCO_3$ present in the blood, and leaves the carbon dioxid uncombined. The subsequent dissociation of the Na and litmus acid enables the litmus acid to generate the blue color. Phenolphthalein is not sufficiently strong to cause such a displacement of the carbon dioxid. For this reason, the titration methods cannot give accurate results concerning the reaction of the blood, but solely regarding the amount of alkalies available for titration.

In addition to such neutral salts as sodium and potassium chlorid and the alkali salts of the proteins of the corpuscles and plasma, the blood also contains a considerable quantity of sodium carbonate. This substance, however, cannot give rise to a decided alkaline reaction, because it is continuously charged with the carbon dioxid of the tissues. In this way, the sodium carbonate is retained in the form of the bicarbonate, during the dissociation of which OH ions are not formed, as is evident from the formula: $NaHCO_3 = Na$ and HCO_3 .

Like other living tissues, blood is practically neutral in reaction and performs its function best when only very faintly alkaline, but naturally, as it serves as the reservoir for the products of metabolism, large amounts of carbon dioxid and other acids are constantly added to it. Under normal conditions, however, any tendency on its part toward an acid reaction is quickly counteracted in the manner indicated. This property of the blood to neutralize acids without acquiring an acid reaction to litmus, is designated as its total alkalinity.

Osmotic Pressure.—As the osmotic pressure is the chief regulatory mechanism by means of which the water content of the tissues is safeguarded, it constitutes one of the most important properties of the blood. Obviously, the normal concentration and composition of the

¹ Höber, Pflüger's Archiv, lxxxi, 1900, 522; P. Fränkel, *ibid.*, xciv, 1903, 601; Henderson, Am. Jour. of Physiol., xxi, 1908, 427, and Michaelis and Davidoff, Bioch. Zeitschrift, xli, 1912, 131.

cells can only be retained, if water and nutritive materials are made to move into them, while their waste-products are made to enter the lymph and blood. Osmotic streams are produced, the intensity of which is directly proportional to the difference in the osmotic pressures between the blood and the tissue-fluid. As these pressures are dependent in turn upon differences in the concentration of the fluids just mentioned, it is of greatest importance that these differences be retained without allowing them to become too great. This condition, however, is not attained without certain changes, because the body is the frequent recipient of large quantities of water and salts and also loses much water and other material through the secretions and excretions.

The osmotic pressure of the blood is determined chiefly by its content in crystalloids, namely the inorganic salts, sugar, urea, and other substances. The proteids, however, cannot be said to be without influence. The most convenient method of measuring the osmotic pressure consists in a comparison of the freezing point of the blood with that of water (value = Δ). A 0.1 molecular solution depresses the freezing point of water 0.186° ; and hence, if the depression which a certain solution is capable of producing, amounts to 0.093° , its concentration must be 0.05 molecular. Again, as the former possesses an osmotic pressure of 2.24 atmospheres at zero, the latter must exert a pressure of 1.12 atmospheres. For ordinary purposes, therefore, the osmotic pressure of the blood may be measured in a simple manner by determining its freezing point with an apparatus such as has been described by Bartley.¹ The freezing point of mammalian blood is about -0.6° C., which figure implies that its osmotic pressure equals $0.6/1.85 \times 22.4 = 7.3$ atmospheres. Under normal conditions only slight variations are observed,² the values for human blood ranging between -0.52 and -0.60 , those for the dog between -0.55 and -0.64 , and those for the rabbit between -0.55 and -0.62 .

Curiously enough, some animals are well-protected against the osmotic pressure of the medium in which they live. The bony fish, for example, possess an osmotic pressure of their body fluids which, in the salt water fish, is lower than that of the sea water and, in the fresh water fish, higher than that of the fresh water. This protection which must be ascribed to a peculiar impermeability to water of the lining cells of the gill-plates, enables these animals to migrate. As a typical example of this kind might be mentioned the salmon which enters the fresh water during the spawning period without suffering injury.

Electrical Conductivity.—This factor depends upon the amount of salts present in the blood, because the passage of an electric current necessitates the presence of dissociated ions. Moreover, as the concentration of the blood varies only within very narrow limits, its conductivity must remain almost the same. It should be emphasized, however, that the corpuscles do not permit the current to pass very readily, because they tend to prevent the ions of the salts carrying the

¹ Archives of Diagnosis, 1913.

² Hamburger, Osmotischer Druck und Jonenlehre, Wisbaden, 1902, 456; Höber, Physik. Chemie der Zelle, 1902, 26; also see: Handb. der Physik. Chemie u. Medizin by Koranyi u. Richter i, 1907, 338.

electric charges, from escaping from the plasma. For this reason, the conductivity of the blood must be attributed largely to the plasma. This is proven by the fact that clear plasma possesses a greater conducting power than plasma to which corpuscles have been added.¹

Viscosity.—When a fluid traverses a straight tube of sufficient length, its different constituents arrange themselves eventually parallel to the long axis of the tube. It is also to be noted that the fluid does not advance as a uniform whole, but unevenly, so that its central core attains a very great speed, while its more external layers progress with a velocity which steadily decreases from within outward. For this reason, the layer next to the wall must remain perfectly stationary provided, of course, that it moistens the internal surface of the tube. In the second place, it should be noted that the individual molecules of the fluid rub against one another, because as the elements in neighboring layers move at different speeds, some of them must be brought

FIG. 96.—FRICTION OF BLOOD.

E, external friction; *J*, internal friction.

in contact with one another, while others are separated from one another. Hence, the movement of a fluid is associated first of all with an external friction arising between its outermost layer and the internal surface of the vessel wall, and secondly, with an internal or intermolecular friction, which, as the name indicates, results between the different bodies held in solution or suspension.

If several different fluids are forced through a narrow tube under a constant pressure and temperature, the quantities obtained of each during a given period of time, varies considerably. For example, if glycerin, water and ether are used, the quantity of ether collected is much larger than that of either water or glycerin. This difference in the readiness with which liquids are capable of traversing a capillary tube, is ascribed to differences in their internal friction. Quite similarly, if blood and water are employed, the former displays a much slower movement than the latter. As can readily be surmised, this tardiness is dependent upon its greater content in solids. Fluids are commonly described as "thick" and "thin," and clearly, the thinner the fluid, the less must be its internal friction. But, besides these purely quantitative differences, fluids also possess certain qualitative peculiarities which impart to them either a "sticky" or a "non-sticky" character. The latter kind of fluid, very naturally, possesses a slighter

¹ G. N. Stewart, *C. Phys.*, xi, 1897, 332.

internal friction, or viscosity. While frequently used as a synonym for the general term of internal friction, the term viscosity should in reality be restricted to that type of friction which has its origin in the qualitative peculiarity of a fluid.

It has been shown by Burton-Opitz¹ that the viscosity of the blood differs greatly in different animals, but remains rather constant in the same group of animals. When compared with distilled water at 37° C.,² the viscosity of human blood is found to be 5.1 times greater, while that of dog's blood is 5.0 times greater. The coefficient for cat's blood is 4.1, for rabbit's blood 3.1, and for the blood of the frog and turtle 2.5. It is evident, therefore, that the viscosity increases with the complexity of the blood, and thus, it may also be inferred that the viscous resistance of the plasma or serum is very much less than that of whole blood. In fact, it is possible to establish perfectly normal degrees of viscosity by simply adding definite numbers of washed red cells to clear serum.

The fact that the viscosity of the blood is subject to variations is shown by the observation that warm baths decrease it, whereas cold baths and exposure of the body to hot air increase it. It is also lessened by hemorrhage and the injection of small quantities of normal saline solution. Arterial blood is less viscous than venous blood; and hence, if a venous character is imparted to the former either by temporarily obstructing the trachea or by permitting the animal to inhale carbon dioxid, its viscous resistance becomes greater than normal. In dyspnea it is increased and also during ether and chloroform narcosis, as well as after the administration of alcohol. It is diminished by starvation and increased by feeding, more especially by the ingestion of proteid material.³

¹ Pflüger's Archiv, lxxii, 1900; cxii, 1906; and cxix, 1908; also Jour. of Physiol., xxxii, 1904 and 1905; Amer. Jour. of Physiol., vii, 1902; and Jour. Exp. Med., viii, 1906.

² The coefficient of the viscosity for distilled water at 37° C. has been determined by Poiseuille (Ann. de Chem. et de Phys., Paris, 1843, Sec. 3, p. 7). Its value is 4700.

³ For clinical purposes the viscosity of the blood is determined with the help of a simple instrument, known as a viscosimeter. An instrument of this kind was first devised by Burton-Opitz (1903). Modifications have been presented more recently by Hirsch and Beck, Hess and Münzer, and Bloch.

CHAPTER XV

THE CHEMICAL COMPOSITION OF THE BLOOD

The Composition of Whole Blood.¹—It must be admitted that it is almost impossible at the present time to obtain exact analytical data regarding the composition of the blood on account of its tendency to coagulate, and, because its composition varies not only in different species, but also in animals of the same group. Besides, considerable divergences may be encountered in one and the same animal, in accordance with the location or functional importance of the vessels from which the blood is withdrawn. Lastly, it is entirely probable that the methods used at the present time are altogether too crude to allow us to detect its more intricate chemical peculiarities.

Under ordinary conditions, human blood contains 77 to 82 per cent. of water, and 18 to 23 per cent. of solids. The latter include 17.3 to 22.0 per cent. of organic and 0.6 to 1.0 per cent. of inorganic material. Proteins and hemoglobin form by far the largest amount of the organic mass; 13 to 15 per cent. being the value for hemoglobin alone. In the ox, sheep, goat, and rabbit the hemoglobin content is lower than in man, while in the dog, horse, cat and pig it is equal to it. The

THE COMPOSITION OF DOG'S BLOOD

	1000 Parts, by weight, of blood contain	1000 Parts, by weight, of serum contain	1000 Parts, by weight, of corpus- cles contain
Water.....	810.050	923.980	644.260
Solids.....	189.950	76.020	355.750
Hemoglobin.....	133.400		327.520
Protein.....	39.680	60.140	9.918
Sugar.....	1.090	1.820	
Cholesterin.....	1.298	0.709	2.155
Lecithin.....	2.052	1.699	2.568
Fat.....	0.631	1.051	
Fatty acids.....	0.759	1.221	0.088
Phosphoric acid: as nuclein.....	0.054	0.016	0.110
Na ₂ O.....	3.675	4.263	2.821
K ₂ O.....	0.251	0.226	0.289
Fe ₂ O ₃	0.641		1.573
CaO.....	0.062	0.113	
MgO.....	0.052	0.040	0.071
Cl.....	2.935	4.023	1.352
P ₂ O ₅	0.809	0.242	1.635
Inorganic:			
P ₂ O ₅	0.576	0.080	1.298

¹ Oppenheimer Handb. der, Biochemie, Jena, 1909.

accompanying table shows the composition of dog's blood as determined by Abderhalden.¹ In another table are given the values for the blood of the horse.

THE COMPOSITION OF HORSE'S BLOOD

1000 Parts of blood contain by weight	1000 Parts of serum contain by weight	1000 Parts of corpuscles contain by weight
Water..... 749.020	Water..... 902.050	Water..... 613.150
Solids..... 250.980	Solids..... 97.950	Solids..... 386.840
Hemoglobin..... 166.900		Hemoglobin.... 315.080
Protein..... 69.700	Protein..... 84.240	Protein..... 56.780
Sugar..... 0.526	Sugar..... 1.176	Sugar..... —
Cholesterin..... 0.346	Cholesterin.... 0.298	Cholesterin.... 0.388
Lecithin..... 2.913	Lecithin..... 1.720	Lecithin..... 3.973
Fat..... 0.611	Fat..... 1.300	Fat..... —
Phosphoric acid as nuclein..... 0.060	Phosphoric acid as nuclein.... 0.020	Phosphoric acid as nuclein... 0.095
Soda..... 2.091	Soda..... 4.434	Soda..... —
Potash..... 2.738	Potash..... 0.263	Potash..... 4.935
Iron oxid..... 0.828	Iron oxid..... —	Iron oxid..... 1.563
Lime..... 0.051	Lime..... 0.1113	Lime..... —
Magnesia..... 0.064	Magnesia..... 0.045	Magnesia..... 0.0809
Chlorin..... 2.785	Chlorin..... 3.726	Chlorin..... 1.949
Phosphoric acid.. 1.120	Phosphoric acid. 0.240	Phosphoric acid 1.901
Inorganic phos- phoric acid.... 0.806	Inorganic phos- phoric acid... 0.0715	Inorganic phos- phoric acid.. 1.458

Sodium chlorid is the chief salt of the serum. It forms 60 per cent. of the ash, while sodium carbonate constitutes about 30 per cent. of it. Traces of the chlorids and phosphates of potassium, sodium and calcium are also present. The chief salt of the corpuscles is potassium phosphate, while that of the plasma is sodium chlorid. In fact, it has been stated that the latter is entirely wanting in the corpuscles of some animals. The potassium content of different corpuscles fluctuates considerably. Chlorin exists in all types of blood, but in greater amounts in the serum than in the corpuscles. Iodin is found only in the serum, while iron appears principally in the erythrocytes, but in small quantities also in the leukocytes. Traces of manganese, lithium, copper, and lead have also been obtained.

Traces of fats, cholesterin, lecithin, dextrose, urea, and other nitrogenous extractives are also present in the serum. The fats in the corpuscles average 0.6 per cent., but this figure may be decreased or increased by feeding. Thus, an increase of ten times the normal value has been obtained by this means in geese, while, in diabetic lipemia, as high a value as 18 per cent. has been found. The fats circulate in the blood in very fine subdivision, the individual globules becoming so numerous at times that a distinct oily or milky appearance is imparted to the blood or to the serum derived from it.

Cholesterin and lecithin are found chiefly in the erythrocytes, nine-tenths of the solids of these cells being formed by hemoglobin and one-tenth by the stroma. In addition to these two substances, the stroma also embraces proteins and salts.

The amount of sugar in the blood varies between 0.1 and 0.15 per cent. and, although somewhat independent of the character of the food ingested, may be greatly increased by feeding. As has been pointed out by Claude Bernard,² sugar

¹ Zeitschr. für Physiol. Chemie, xxv, 1898, 88.

² Lecons sur la diabète, Paris, 1877.

makes its appearance in the urine (glycosuria), when present in the blood in larger amounts than 0.3 per cent.¹ Sugar is not a constituent of the corpuscles.

The urea content of the blood varies between 0.02 and 0.15 per cent. It increases after the ingestion of meat and decreases during starvation.² In normal human blood, von Jaksch,³ found this body in amounts of 0.05 to 0.06 per cent. An augmented protein metabolism or a retarded elimination of urea leads to an accumulation of these substances in the blood. Traces of ammonia are also present. The quantity of lactic acid varies considerably; as much as 0.071 per cent. has been found.

The Constituents of the Blood Plasma.—The liquid which serves as the medium for the corpuscles, may be obtained by rapid centrifugalization, or by rendering the blood non-coagulable and permitting the formed elements to settle. The supernatant portion of the blood may be made to clot at any time by the addition of an agent possessing the power of inciting coagulation. The clotting of the blood may be said to be chiefly dependent upon the plasma, because the latter contains all the substances essential for this process.

The plasma is yellowish in color, alkaline in reaction, and possesses a specific gravity of about 1.026 to 1.029. Its composition per 1000 parts is as follows:

Water.....	902.90
Solids.....	97.10
Proteins:	
Fibrin.....	4.05
Other proteins.....	78.84
Extractives (including fat).....	5.66
Inorganic salts.....	8.55

Sodium chlorid is most abundant in human blood plasma. It forms 60 to 90 per cent. of the total mineral matter. Schmidt gives the following table for each 1000 parts of plasma:

Mineral matter.....	8.550
Chlorin.....	3.640
SO ₃	0.115
P ₂ O ₅	0.191
Potassium.....	0.323
Sodium.....	3.341
Calcium phosphate.....	0.311
Magnesium phosphate.....	0.222

In general, it may be said that plasma contains 10 per cent. of solids of which 8 per cent. are in the form of proteins. The latter are classified as fibrinogen, serum-globulin, paraglobulin and serum-albumin. Albumoses or peptones are not present. Inasmuch as the plasma of coagulating blood separates into fibrin and serum, the proteins contained therein, may be divided into those apportioned to the fibrin and those contained in the serum. Among the former we have fibrinogen, thrombogen, and kinase. The serum embraces proteins,

¹ E. L. Scott, *Am. Jour. of Physiol.*, xxxiv, 1914, 271. (Literature.)

² Schöndorff, *Pflüger's Archiv*, liv, 1893, and lxiii, 1896, 192.

³ *Festschrift für v. Leyden*, i, 1901.

extractives, and salts. The first of these embrace serum-globulin, serum-albumin, fibrin-ferment and nucleoprotein.

Blood Serum.—The serum is a sticky liquid, the specific gravity of which varies between 1.027 and 1.032; its average value is 1.028. Toward litmus it exhibits an alkaline reaction which is somewhat greater than that of the plasma. Its color is faintly yellow, shading into green. While clear under ordinary conditions, it may become cloudy or milky in consequence of its admixture with varying amounts of fat. The yellowish coloring material ordinarily present in fats, to which the appearance of the serum is due, is generally called lutein or lipochrome.

The quantity of the cellular material ordinarily found in serum, varies between 7.0 and 9.7 per cent. The bulk of the latter is formed by proteins in amounts of 5.5 to 8.4 per cent. The average depression of the freezing point of blood-serum is given as $\Delta = -0.526^\circ$, as against that of whole blood which is $\Delta = -0.537^\circ$. The following analytical data pertaining to serum have been supplied by Abderhalden:

Water.....	913.64
Solids.....	86.36
Protein.....	72.50
Sugar.....	1.05
Cholesterol.....	1.238
Lecithin.....	1.675
Fat.....	0.926
Phosphoric acid as nuclein.....	0.0133
Soda.....	4.312
Potash.....	0.255
Iron oxid.....	
Lime.....	0.1194
Magnesia.....	0.0446
Chlorin.....	3.69
Phosphoric acid.....	0.244
Inorganic phosphoric acid.....	0.0847

The Proteins of the Blood.—*Fibrinogen*, the mother-substance of fibrin, is associated with serum-globulin and serum-albumin (page 216). *Serum-globulin* is also called paraglobulin, serum-casein, or fibrinoplastic substance. Besides being present in plasma and serum, it is also found in lymph, transudates and exudates, as well as in the corpuscles and several tissues of the body. The probability is that serum-globulin is not a separate substance, but consists of several protein bodies. Their complete separation, however, has not been effected as yet. Hammarsten states that its average composition is: C 52.71, H 7.01, N 1.585, S 1.11, O 23.02. According to Schmiedeberg, its molecular composition is: $C_{117}H_{182}N_{30}SO_{38} + \frac{1}{2}H_2O$. The blood of different animals contains different amounts of this substance; for example, that of the rabbit 1.78 per cent., that of man 3.10 per cent., and that of the horse 4.56 per cent. Serum is said to contain a larger amount of this substance than plasma, the surplus being derived from disintegrated leukocytes.

The globulins are usually obtained by half-saturation of the serum

with ammonium sulphate. They may also be gotten by dialysis with distilled water. As globulin is insoluble in distilled water, it is precipitated. The latter method yields a smaller quantity than the former, and hence, two types of globulins have really been isolated, namely euglobulin, and pseudoglobulin. The latter is the one that is thrown down during half-saturation with ammonium sulphate.

Serum-albumin is found in plasma, serum, lymph, transudates, exudates, and other animal fluids. It remains in the serum after half-saturation with ammonium sulphate, but is precipitated by complete saturation. It may also be prepared in crystalline form by the method of Gürber. From neutral or acid solutions it is isolated by heating to 70°–75° C.; in fact, it has been stated that three heat precipitations occur, namely one at 73°, one at 77° and one at 84°C. This fact has been thought to prove that serum-albumin is a mixture of three proteins. However that may be, it may be assumed for the present that two protein bodies enter into its formation. According to Michel,¹ its composition is: C 53.08, H 7.10, N 15.93, S 1.90, O 21.96, and its molecular composition, as represented by Schmiedeberg:² $C_{78}H_{122}N_{20}SO_{24}$. The amount of this body ordinarily found in the blood of the horse equals 3.67 per cent. and in human blood 4.52 per cent.

Thrombogen, or inactive thrombin, is prepared by adding an excess of alcohol to serum. A precipitation of the proteins and thrombin results; the latter, however, is not so easily coagulated by alcohol as the proteins.

The extractives embrace nitrogenous and non-nitrogenous material. The former consists of urea and small quantities of uric acid, creatin, creatinin, xanthin, hypoxanthin, and amino acids. The latter comprises fats, soaps, cholesterin, and sugar.

CHAPTER XVI

THE RED BLOOD CORPUSCLES

A. PHYSICAL CHARACTERISTICS

Shape, Size and Color.—With the exception of the camelidæ, the mammalian red corpuscle,³ when placed flat upon the slide, possesses the shape of a circular platelet, and, when turned on edge, that of a

¹ Verh. der phys. med. Gesellsch. zu Würzburg, xxix, No. 3.

² Archiv für Exp. Path. und Pharm., xxxix, 1897, 1.

³ The red corpuscles of the frog were first observed by Swammerdam in 1658 and those of the mammal by Malpighi in 1661. They were first described by van Loewenboek in 1673.

dumb-bell.¹ Its thin central area is surrounded by a thick marginal zone. When the latter is brought into focus, the center appears dark, because its focal point lies at this time at a lower level. When cir-

FIG. 97a.—HUMAN RED CORPUSCLE PLACED FLAT AND ON EDGE.

FIG. 97b.—RED CORPUSCLE OF FROG PLACED FLAT AND ON EDGE.

culating through the vascular channels, the fully developed red cell does not contain a nucleus; in fact, the loss of this constituent very shortly after the cell has entered the blood-vessels, is generally con-

FIG. 98.—AREA OF CAPILLARIES.

Showing tubules of different diameter, some so small that the red cells cannot enter at all and others through which they can only pass by assuming an elliptical outline.

sidered as the cause of the central depression. In the camels, the red corpuscle presents an elliptical outline, but resembles the preceding

¹ Weidenreich, Lewis, Radasch and others hold that the red corpuscles assume this shape only in shed blood and are cup-shaped or bell-shaped while circulating. This change is said to be caused by cooling and evaporation. Jordan, who has reinvestigated this subject more recently, states that a freely moving corpuscle always shows a central depression. (Proc. Soc. Exp. Biol. and Med., xii, 1915.) Viewed from the side, however, these biconcave discs give the impression of shallow cups, because the pressure tends at times to cause them to bulge out centrally.

type in all other particulars. In other vertebrates,¹ it is elliptical² and contains a very conspicuous nucleus. It is soft and very elastic, peculiarities which enable it to traverse capillary channels of smaller diameter than its own. In these minute tubules the otherwise circular discs often assume a shape approximating the elliptical.

The size of the red cell differs greatly in different animals, but varies only very slightly in animals of the same group. In man it measures $7.5\mu^3$ in diameter (7.1 to 7.8μ) and 1.6μ in thickness. Its volume equals 0.000,000,072 c. mm. Variations in size between 6.5 and 9.3μ have been noted even in normal persons. Elliptical corpuscles have been found in a few individuals. The following compilation will show that red corpuscles are in existence which are either very much smaller or larger than the human.⁴

Circular corpuscles		Elliptical corpuscles	
Musk-deer.....	2.3μ	Lama.....	$7.5 \times 4.2\mu$
Goat.....	4.25μ	Pigeon.....	$14.7 \times 6.5\mu$
Sheep.....	5.0μ	Frog.....	$23.0 \times 16.3\mu$
Horse.....	5.5μ	Triton.....	$29.5 \times 19.5\mu$
Pig.....	6.0μ	Proteus.....	$58.2 \times 35.6\mu$
Cat.....	6.2μ	Amphiuma.....	$77.0 \times 58.0\mu$
Rabbit.....	7.1μ		
Dog.....	7.2μ		
Man.....	7.5μ		
Ox.....	8.0μ		
Elephant.....	9.4μ

FIG. 99.—CIRCULAR RED CORPUSCLES DRAWN TO SCALE.

M, musk-deer; G, goat; P, pig; M₁, man; O, ox; E, elephant.

ished or prevented altogether by adding normal saline solution, or some other non-destructive medium to the blood.

¹ In lamprey eels the corpuscles are round, biconcave and nucleated.

² Not oval, because this term implies that one of the ends is more pointed than the other.

³ 1μ (micron) equals 0.001 mm.

⁴ Monassein, Dissertation, Berlin, 1872; and Schilling—Torgau, *Folia hematologica*, i, 1912.

Variations in Shape.—Although it is claimed by Schultze¹ that the erythrocytes of the chick possess active motion, it seems that the red blood cells of the mammals remain perfectly passive as long as the fluid in which they are kept, retains its normal character. But their form may be changed at any time by varying the temperature or the carbon dioxid content of the medium, or by permitting an electrical current to pass through them. Most generally, they react to

FIG. 100.—HUMAN BLOOD-CORPUSCLES ARRANGED IN ROULEAUX. (Funke.)

these changes by increasing their volume. Moreover, Cavazzani has shown that if blood is collected in an isotonic or hypotonic solution of sodium chlorid to which potassium ferrocyanid has been added, the red corpuscles of man and other animals send out delicate protoplasmic processes, the rapid motion of which enables them to move about from place to place. If a drop of cocain hydrochlorid is then added to this solution, these filaments are retracted within a few moments.

FIG. 101.—POIKILOCYTES.

1 and 2, Mulberry shape; 3, prickly pear shape; 4, shadow.

Changes in the size of the red corpuscles are frequently observed in disease. Cells possessing a diameter of about 6μ are found in anemia, while cells with a diameter of 10μ and over are encountered in persons suffering from pernicious anemia, leukemia, chlorosis or cirrhosis of the liver. The former are known as *microcytes* and the latter as *megalocytes* or *macrocytes*. When both their size and shape are

¹ Archiv für mikr. Anat., i, 18.

altered, they are designated as *poikilocytes*. The latter usually exhibit pointed projections, like burs, or surfaces beset with rounded elevations.

Number of the Red Blood Corpuscles.—While the method for the counting of the red cells, devised by Vierordt¹ and Welker² has been modified by different authors, the principle involved in it has remained the same. The instrument most commonly used to-day is the hemo-

FIG. 102.—HEMOCYTOMETER. (Thoma-Zeiss.)

A, pipet; B, glass bead; C, counting chamber seen from side; D, counting chamber seen from above; E, field as seen under microscope.

cytometer of Thoma-Zeiss.³ It consists of a pipet (A), originally devised by Potain, and a counting chamber (C). Having thoroughly cleansed the skin upon the tip of the finger or upon the lobule of the ear, a small wound is made with a lancette or needle. A portion of the blood collected upon the integument is then quickly drawn into the

¹ Arch. für physiol. Heilkunde, xiii, 1854, 259.

² Prager Viertelj. für prakt. Heilkunde, iv, 1854.

³ See Abbé: Sitzungb. d. Jenaischen Gesellsch. f. Med., 1878; also see: Bürker, Handwörterb. der Naturw., Jena, 1912; and Hayem, in Sahli's Lehrb. d. klin. Untersuchungsmethoden, Leipzig, 1909.

pipet until either point 0.5 or 1 has been reached. The end of the pipet is then dried with filter paper and immediately dipped into an isotonic solution¹ which is intended to dilute the blood previously drawn in. The tube is then filled to point 101 above its bulbular enlargement. Upon its withdrawal from the fluid it is again dried with filter paper and gently shaken until the blood and the solution have become thoroughly mixed. The marks upon the tube signify that if the blood is drawn in as far as point 1 and the diluting fluid as far as point 101, the original sample of blood is diluted 100 times, whereas, if the marks 0.5 and 101 are used, a dilution of 200 times is the result.

Having thoroughly mixed the contents of the pipet, a drop or two are permitted to escape from the tube without being used. The next droplet, however, is collected upon the stage of the counting chamber (C) and in such a manner that it does not overflow into the space next to it. The entire compartment is then closed by placing a cover-glass over it. The surface of the stage is exactly 0.1 mm. below the lower surface of the cover-glass. A series of 20 squares are engraved upon the former, the sides of which measure $\frac{1}{2}_0$ mm. in length, and hence, each possesses an area of $\frac{1}{4}_{00}$ sq. mm. and a capacity of $\frac{1}{4}_{00} \times 0.1 = \frac{1}{4}_{000}$ cu. mm. Having counted the number of corpuscles in many of these small squares, a fair average value is obtained from these figures. The value so obtained is then multiplied by the degree of dilution and by 4000.

It is only natural to suppose that the size and number of the red corpuscles must preserve an indirect relationship to one another. That this is true, is borne out by the following table² which should be compared with the one containing the data pertaining to the size of the different red cells.

¹ Various preserving solutions have been recommended, for example:

(a) Hayem's fluid:

Hydrarg. bichlor.....	0.5 gram.
Sodii sulphat.....	5.0 grams.
Sodii chlorid.....	2.0 grams.
Aq. distill.....	200.0 c.c.

(b) Gower's fluid:

Sodii. sulphat. gm.....	104.0
Acid acetic.....	3i
Aq. destill.....	g. s. ad. 3iv

(c) Toisson's fluid:

Aq. destill.....	160.0 c.c.
Glycerin.....	30.0 c.c.
Sodii sulphat.....	8.0 grams.
Sodii chlorid.....	1.0 gram.
Methyl violet.....	0.025 gram.

² Storch, Unters. über den Blutkörperchengehalt des Blutes, etc. Dissertation, Bern, 1901; Musser and Krumbhaar, Folia hematologica, xviii, 1914, 576, and Wells and Sutton, Am. Jour. of Physiol., xxxix, 1915, 31.

	Mill. per c.mm.
Goat.....	14-19
Lama.....	13-13.2
Sheep.....	10.3
Cat.....	9.1
Horse.....	7.8
Monkeys.....	6.2
Rabbit.....	6.8
Dog.....	6.7
Birds.....	2.3
Fish (bony).....	1.2
Reptilia.....	0.5-1.6
Amphibia: frog.....	0.5
Salamander.....	0.09

The average number of red corpuscles in one cubic millimeter of human blood is given as 5,000,000; in woman, however, their number is somewhat smaller, namely, about 4,500,000. In infants a higher count is usually obtained than in adults. During the first weeks it averages about 5,580,000, during the first and second years 5,680,000, and from the second to the sixth year seldom under 5,900,000. Since the volume of a red cell measures 0.000000072 cu. mm. and its surface 0.000128 sq. mm., the total surface of the red blood corpuscles present in 1.0 cu. mm. of blood, must equal 640 sq. mm. Moreover, if the blood contained in a mammal is calculated at $\frac{1}{13}$ of its body weight, an individual weighing 70 kg. must contain about 5 kg. of blood. The body as a whole, therefore, gives lodgment to about 25,000,000,000,000 red cells, possessing a total surface of 3200 sq. mm. which equals an area 1500 times greater than that of the surface of the body.¹ These figures clearly betray the surprisingly large size of the "breathing surface" which the red corpuscles present to the air in the lungs or to the cells of the tissues.

Variations in the Number of the Red Blood Corpuscles.—While the value of 5,000,000 cells to the cubic millimeter of blood remains fairly constant under normal conditions, it is subject to certain minor fluctuations. Ordinary physical influences, for instance, possess the tendency of diverting the corpuscles into the larger vascular channels, while the blood in the peripheral vessels contains them in somewhat smaller numbers. This fact should be taken into account whenever these bodies are counted in accordance with the method previously described. It is also to be remembered that a diminution in the quantity of the body-fluids may result at any time in consequence of a lessened intake of water, or on account of a more copious discharge of it in the sweat, stools or transudations. In either case, the number of corpuscles per unit of blood must become greater. The reverse result is obtained if large quantities of water are taken in, or if smaller amounts are excreted. In early fetal life the red cells are fewer in

¹ Recent investigations have shown that in man the total amount of blood should be calculated at one-twentieth of the body weight. The total surface of the red cells, therefore, measures 1700 sq. mm.

number; namely, only 0.5 to 1.0 million per cubic millimeter. Their number increases later on so that infants present higher values than the average for adults. Pregnancy causes a slight increase and menstruation a decrease. Physical exertion at low altitudes causes a concentration of the blood which Schneider and Havens¹ attribute to the sudden passage into the blood of a large number of red corpuscles which have been lying dormant in the body, chiefly in the splanchnic area. Scott² believes this concentration to be effected by a passage of fluid from the blood to the tissues, in consequence of the higher blood-pressure coincident with muscular exercise. Massage, and especially massage of the abdomen, produces a similar effect for the same reason. During hibernation the number of the red corpuscles is not materially changed. Neither is the specific gravity of the blood, whereas the number of the white cells is decreased to about one-half of normal.³

A very interesting phenomenon is the increase in the number of the erythrocytes, resulting whenever high altitudes are attained. Bert⁴ and Viault,⁵ who first studied this change, have found that the inhabitants of low lands show this increase whenever they ascend a high mountain and that persons permanently residing in a mountainous country, constantly give counts above normal. It is then not unusual to obtain increases to as much as 7,000,000 or 8,000,000 per cu. mm., but in most cases the maximal value is not attained until about twenty-four hours have been spent at the high altitude. According to Kemp,⁶ the number of the platelets is also increased, but the leukocyte count remains the same.

Two possibilities present themselves, namely, it is conceivable that this increase is dependent upon a greater formation of red cells by the hematopoietic tissues or secondly, that it is due to changes in the quantity of the blood plasma. The second view, originally expressed by Grawitz,⁷ embodies the possibility that the sojourn in mountainous regions leads to a concentration of the blood, because the greater respiratory activity coincident with muscular exertion and sweating, occasions a loss of a considerable quantity of water. Gaule, Hallion and Tissot, however, have shown that an increase in the number of the red cells also appears during balloon ascensions, and hence, muscular efforts cannot be considered as the cause of this phenomenon. Abderhalden⁸ and Bunge,⁹ who also believe that the increase is only an apparent one, assert that the blood is really made

¹Am. Jour. of Physiol., xxxvi, 1905, 239.

²Ibid., xlv, 1917, 298.

³Rasmussen, Ibid., xli, 1916, 465.

⁴La pression barométrique, Paris, 1878, or Compt. rend., xciv, 1882, 805.

⁵Compt. rend., cxi, 1890, 917.

⁶Am. Jour. of Physiol., x, 1904, 34.

⁷Berliner klin. Wochenschr., xxxii, 1895, 743.

⁸Zeitschr. für Biol., xliii, 1902, 423.

⁹Verhandl. des Kongr. f. innere Med., xliii, 1895, 192.

"plasma-poor," because a considerable portion of its fluid mass is transferred into the perivascular lymph-spaces.¹

The first view, that the increase is real and is caused by a greater formation of red cells, possesses the advantage of being more closely in keeping with physiological facts, but it must be admitted that it has not been possible so far to ascertain the stimulus which gives rise to the greater activity of the corpuscle-forming organs. Indeed, it is entirely probable that several factors unite in bringing this change about.² The most interesting of these is the influence which the barometric pressure exerts upon the interchange of the gases in the lungs. As the high altitude is reached, the tension of the gases is diminished and particularly, the pressure which ordinarily forces the oxygen to combine with the hemoglobin of the red corpuscles. The oxygen poverty of the tissues resulting in consequence of the deficiency in the tension of this gas, eventually serves as a stimulus to intensify the production of these corpuscles. Thus, while each cell is charged with a somewhat smaller quantity of oxygen than normal, the total amount of this gas in the body must remain practically the same, because the number of its carriers has been augmented. In substantiation of this explanation, it might be mentioned that Dallwig, Kolls and Loevenhart³ have succeeded in demonstrating that considerable increases in the number of the erythrocytes also occur in dogs, rabbits, and cats, when kept in an atmosphere of low oxygen concentration even at atmospheric pressure and under conditions which do not require physical efforts.

A decrease in the number of the red corpuscles is frequently encountered in disease (oligocythemia). Anemias from all causes are characterized by a change of this kind, and clearly, this decrease must be due either to a greater destruction or to a lessened formation of these cells, or both. A very pronounced diminution in the number of the erythrocytes is frequently observed in pernicious anemia, counts of 300,000 to 400,000 per cu. mm. being not uncommon. Great numbers of red corpuscles are lost in hemorrhage, which it may take days and weeks to replace. Naturally, an acute hemorrhagic anemia, or, more correctly speaking, an oligemia, is followed by a greater production of red cells, but the activity of the corpuscle-forming organs has its natural limits and is therefore relatively slow. The fluid parts of the blood, on the other hand, are replaced very quickly, this end being attained by a lessened discharge of fluid from the body and a transfer of lymph into the chief circulatory system. In this way, an initial hydremia is frequently developed. Furthermore, even if the number of the red cells has again risen to normal, their hemoglobin content may remain below normal for some time to come. A chlorotic condition of a temporary kind may thus be developed. Marked increases in the number of the red cells are noted at times in active pathological conditions, but the hemoglobin content need not be augmented in a corresponding measure. This condition in which counts of 7,000,000 to 8,000,000 per cu. mm. are encountered, is designated as polycythemia.

¹ The assumption that changes in barometric pressure incite variations in the capacity of the counting chamber, has been disproved by Bürker.

² As additional exciting causes are regarded changes in temperature and cutaneous stimuli (Schumburg and Zuntz; Pflüger's Archiv, lxiii, 1896, 461).

³ Am. Jour. of Physiol., xxxix, 1915, 77.

B. CHEMICAL PROPERTIES

The Composition of the Red Corpuscles.—Different varieties of red cells contain between 57 and 65 per cent. of water and between 35 and 43 per cent. of solids. It may be said in general that they yield 65 per cent. of water and 35 per cent. of solids. The latter consist of hemoglobin, 33 per cent., protein, 0.9 per cent., cholesterin and lecithin, 0.46 per cent., and inorganic salts, such as potassium phosphate and chlorid and sodium chlorid, 1.4 per cent. Hence, the hemoglobin forms by far the largest portion of the total solids, namely, 94 per cent.

Each red corpuscle is composed of a reticular network, or stroma, and a fluid or semifluid portion. The former appears as a delicate spongy and colorless ground substance, in the spaces of which is deposited the hemoglobin, together with a small quantity of water and salts. The hemoglobin exists here in a peculiar amorphous condition and is not held in solution, nor is it deposited in crystalline form.

Separation of the Stroma and Hemoglobin. Hemolysis.—The procedures usually employed to isolate the hemoglobin are quite simple. The blood may be frozen and thawed several times in succession, or it may be diluted with a small quantity of distilled water. It also suffices to add to it a small amount of ether, chloroform, solanin, saponin, alkalies or bile acids. Of special interest are those bodies which are normally present in some animals and plants and which, when brought in contact with blood, cause a destruction of the red cells and a liberation of their hemoglobin. This process is known as hemolysis, while the agents concerned in it are designated as hemolysins. These bodies are found in the products of bacteria, as well as in the venoms and irritating secretions of snakes, toads, bees, and spiders. They also exist in the normal blood-sera of the higher animals in which they play an important part in the production of immunity. The hemoglobin is liberated by them either by causing the corpuscles to rupture or by abstracting this substance from them without marked injury to their framework. The former change may be produced by placing the corpuscles in water, and the latter by adding such solvents as ether or chloroform to the medium in which they are kept. A very rapid, almost explosive, destruction is had if they are brought in contact with bile. When subjected to any one of these agents, the blood gradually assumes a much darker color and becomes more transparent, this change in its appearance being indicative of the escape of the hemoglobin and its free dissemination through the plasma. The stromatic remnants of the corpuscles are then designated as "shadows," and the blood as a whole as "laked" blood.

In order to retain the volume and shape of the red cells for a long period of time, it is necessary to place them in a medium which is absolutely isotonic to them, or, in other words, in a solution which possesses the same concentration and, therefore, also the same osmotic pressure as the blood-serum. The fluid most commonly

employed for this purpose is a solution of sodium chlorid, the strength of which must be varied somewhat in accordance with the type of the red cell to be preserved. Thus, it is best to employ it in strengths of 0.85 to 0.9 per cent. for the corpuscles of human blood and in a strength of 0.8 per cent. for those of ox blood; in fact, the erythrocytes of the frog require an even weaker solution, namely, 0.70 to 0.75 per cent. It should not be forgotten, however, that it is difficult to keep a medium of this kind in a perfectly isotonic condition for any length of time, because a certain loss of water by evaporation cannot be avoided, and naturally, as the solution becomes more concentrated, it incites such alterations as are usually produced by hypertonic solutions of any kind.

For purposes of transfusion a 0.75 per cent. solution of sodium chlorid, commonly designated as "normal saline," is generally made use of. More favorable results may be obtained at times by employing the so-called Ringer's solution which contains the chlorids of sodium, potassium and calcium in the following proportions:

Sodium chlorid.....	0.9 per cent.
Calcium chlorid.....	0.026 per cent.
Potassium chlorid.....	0.03 per cent.

Under normal conditions, therefore, the blood plasma and the corpuscles are in a state of osmotic equilibrium, and while water passes into them constantly, an equal amount of the latter is again discharged into the plasma. In this way, these two neighboring osmotic entities are enabled to retain the same concentration, and hence, a destruction of the red cells cannot take place. But, naturally, if the concentration of the plasma is either increased or decreased, the osmotic equilibrium is immediately disturbed. If increased, the plasma acts as a hypertonic solution and if decreased, as a hypotonic solution. In either case, the change in its concentration insures an alteration in its osmotic pressure, which immediately gives origin to certain interchanges between it and the contents of the corpuscle. Obviously, the purpose of this transfer is to reestablish an osmotic balance. Thus, if the medium is hypertonic, molecules of water will continue to leave the corpuscles, until the latter eventually become greatly reduced in size and uneven in outline. Conversely, a hypotonic medium will cause water to pass into the corpuscles until they become much distended and finally rupture, giving rise to a great variety of abnormal shapes.

The red cells are regarded by some authors as small bags containing a concentrated solution of hemoglobin. The latter is said to diffuse out whenever the enveloping membrane is changed in such a way that it becomes more permeable to this substance. It must be doubted, however, that this explanation is correct, because the red corpuscles do not possess a true cellular membrane enclosing a free space, and because the hemoglobin actually forms an intricate part of the stroma. Hence, the hemoglobin must first be separated from the latter, either by mechanical or chemical means, before its escape from the cell can be effected. Obviously, a red cell cannot be compared with a receptacle of water which, on breaking, discharges its contents in all directions.

In order to separate the stroma from the hemoglobin, it is best either to defibrinate the sample of blood or to render it non-coagulable by the addition of potassium oxalate. It is then placed in the centrifuge. When completely separated, the corpuscular elements are washed repeatedly in 10 to 20 volumes of a 1 to 2 per cent. saline solution until free from serum. On addition of 5 to 6 volumes of distilled water containing a small amount of ether,¹ the corpuscles swell up and discharge their hemoglobin into the surrounding medium. Centrifugalization is resorted to in order to accelerate the deposition of the leukocytes. The supernatant fluid is treated with a 1.0 per cent. solution of KHSO_4 until it acquires the same

¹ Wooldridge, Archiv f. Anat. u. Physiol., 1881, 387.

density and appearance as the original sample of blood. The stroma is then thrown down by centrifugalization and may be collected upon a filter and quickly washed with distilled water. When free from hemoglobin, the stroma possesses poisonous properties, and gives rise to intravascular clotting.

The constituents of the stroma are lecithin, cholesterin, nucleo-albumin and a globulin. The stroma protein forms about 4 per cent. of the total solids of the red cell and is easily dissolved by dilute alkalis although insoluble in dilute acids.

Great importance is attached to the presence in the red corpuscles of lecithin and cholesterin which substances constitute as much as 30 per cent. of the dry weight of the stroma. Whether these bodies are held solely in the surface layers or are contained within the meshes of the stroma is still doubtful, but it has been ascertained that they determine the permeability of the corpuscle and are, therefore, directly responsible for the osmotic interchanges between it and the plasma. The red cells are completely impermeable to the ordinary varieties of sugar, marmite and arabite, while water, acids, alkalis, ether, esters, urea and bile salts are freely admitted. Amino-acids do not enter very readily.

The Constituents of Hemoglobin.—The normal circulating blood contains the hemoglobin either in the form of oxyhemoglobin or “reduced” hemoglobin. The latter is generally called hemoglobin, because the term “reduced” is prone to convey the erroneous impression that it has been formed by a true chemical decomposition. As the name indicates, oxyhemoglobin is more fully charged with oxygen and is found, therefore, in the arterial blood, while hemoglobin proper is the normal constituent of the blood returned from the tissues.

As the function of hemoglobin is to serve as a storehouse and carrier of oxygen, it may be inferred that it is widely distributed throughout the animal kingdom. It really plays the part of the chlorophyll of the plants. It is of interest to note that it is not always confined to the blood, but is also found in several tissues, for example, in the striated and cardiac muscle cells of mammals, and in several other tissues of the lower animals. It should also be remembered that it is not always held in the corpuscular elements but may be dissolved in the plasma. The ordinary coloring pigments, such as exist in the hair, choroid coat of the eye, and other structures, are not allied to hemoglobin, at least not functionally.

Hemoglobin belongs to the compound proteids. When decomposed in the absence of oxygen, it yields a protein called globin and a coloring matter designated as hemochromogen. The latter forms about 4 per cent. of the molecule. It contains iron and may be oxidized into a more stable body, known as hematin. The latter can also be obtained in a more direct manner by subjecting the hemoglobin to the action of acids or alkalis.

The composition of oxyhemoglobin differs somewhat in different animals, a fact which suggests that it is subject to slight modifications. The following analyses fully illustrate this point:

	Horse	Ox	Pig	Dog	Squirrel	Hen
C.....	54.87	54.66	54.71	53.85	54.09	52.87
H.....	6.97	7.25	7.38	7.32	7.39	7.19
N.....	17.31	17.70	17.43	16.17	16.09	16.45
S.....	0.65	0.44	0.47	0.39	0.40	0.85
Fe.....	0.47	0.40	0.39	0.43	0.59	0.33
O.....	19.73	19.54	19.60	21.84	21.44	22.50
	(Kossel)	(Hüfner)			(Hoppe-Seyler)	

According to Jaquet, the molecular formula of hemoglobin is $C_{758}H_{1203}N_{195}S_3FeO_{218}$, with a molecular weight of 16.66 grams. Its molecule, therefore, is extremely large and complex, a peculiarity which Bunge explains by saying that, as iron is eight times as heavy as water, it must be united with a very large organic molecule, otherwise it could not be floated by the blood. The pigment substance hematin, on the other hand, possesses a relatively simple constitution, as may be gathered from the following formula of Küster, which reads: $C_{34}H_{34}N_4FeO_5$.

The Preparation and Quantity of Oxyhemoglobin.—If blood is laked and is then allowed to stand, the dissolved hemoglobin is deposited in time in the form of crystals. It is to be noted, however, that

FIG. 103.—HEMOGLOBIN CRYSTALS. (After O. Funke.)

the speed with which they are formed varies considerably. Thus, they appear very rapidly in the laked blood of the horse, dog and guinea-pig, and especially if the sample of blood is cooled to $-10^{\circ}C.$, or if a small quantity of alcohol is added to it. The blood of the pig, ox, or man yields them with much greater difficulty. Better results may be obtained if the sample of blood is first diluted with an equal quantity of a saturated solution of ammonium sulphate. The precipitate, which consists of globulins, is then filtered off and the filtrate permitted to stand. The methods most commonly employed for

the isolation of these crystals, are those described by Hoppe-Seyler as well as by Reichert and Brown.¹

The crystals so obtained are red in color and transparent. Although their size is generally microscopic, they may attain a length of 2 to 3 mm. They appear as prisms, platelets, tetrahedra and needles of the rhombic system. From the blood of squirrels six-sided plates of the hexagonal system are usually obtained; moreover, it is possible to change these into rhombic prisms and tetrahedra by the process of recrystallization. They may be heated to 110–115° C. without decomposition, but when subjected to a temperature of about 160° C., a reduction results, the ash yielded during this process being composed largely of oxid of iron. They are soluble, but not in an equal measure, because those most difficult to produce are most readily dissolved. Very dilute solutions of the carbonates of alkalis are the most efficient solvents. Hemoglobin is not easily dialyzed. It does not diffuse through parchment membranes and shows a behavior similar to that of colloidal bodies.

Reduced hemoglobin is more soluble than oxyhemoglobin. Its crystals are not easily obtained. They are isomorphous to the corresponding crystals of oxyhemoglobin and are darker in color and pleochromatic.

The hemoglobin content of the blood amounts to about 14 per cent. in man and to 13 per cent. in woman. Thus, an individual weighing 70 kilos, contains about 2684 grams of blood and about 491 grams of hemoglobin. This amount is distributed among 25,000,000,000,000 red corpuscles which present a total surface of about 3200 square meters. Moreover, as these bodies are usually well scattered and traverse the capillaries almost "in single file," practically all of the hemoglobin is made available for respiratory purposes. It is also of interest to note that blood absorbs a much greater quantity of oxygen than water. Thus, while 100 c.c. of the latter take up only 0.7 c.c., 100 c.c. of human blood assimilate 18.5 c.c. of this gas. The amount of hemoglobin present in the blood of the fetus or infants, is much greater than that found in the blood of adults.

Properties of the Compounds of Hemoglobin with Oxygen.—The function of hemoglobin, to distribute the oxygen to the different tissues of the body, depends upon its ability to unite with perfectly definite amounts of this gas. This union takes place in the lungs, where this substance is exposed to the full pressure of the oxygen of the atmospheric air. Having absorbed its quota of the gas, it is moved onward to the distant tissues. Here the oxygen is required for purposes of oxidation, and hence, inasmuch as it is present in smaller amounts in the cells than in the blood, it must be held under a greater partial pressure in the blood-vessel than in the tissue. As a direct result of this difference in its partial pressure, it separates from the hemoglobin and enters the cells. The oxyhemoglobin is thus converted into its deoxidized or reduced variety. This property of the hemoglobin to assimilate and to release a part of its oxygen, forms the basis of the respiratory activity of the blood.

The compound of hemoglobin and oxygen, known as oxyhemoglobin, can also be formed and destroyed outside of the body. Thus, if arterial blood is exposed to a vacuum, it frothes and its color changes to bluish red in accordance with the amount of oxygen withdrawn from it. Quite similarly, if venous blood is shaken

¹ The characteristics of the crystals of hemoglobin from different animals are described by Reichert and Brown, in: *The Crystallography of Hemoglobins*, Carnegie Inst. of Washington, No. 116, 1909.

in air or pure oxygen, it gradually assumes a much lighter color, because its hemoglobin is thereby converted into oxyhemoglobin. These changes may be considerably hastened by warming the blood. The conversion of oxyhemoglobin into hemoglobin may also be attained by adding a reducing agent to the blood. Such agents as ammonium sulphid, an ammoniacal solution of ferrous tartrate or hydrazin, are commonly employed.¹

The power of hemoglobin to combine with oxygen seems to depend upon the iron which it contains. The figures given above show that the amount of iron varies only very slightly, and hence, the quantity of hemoglobin may be ascertained by simply determining the iron content of the blood. One atom of iron corresponds to about two atoms or one molecule of oxygen.

Methemoglobin.²—This body is a compound of hemoglobin and oxygen which does not occur normally in the body. It appears whenever large amounts of hemoglobin are set free in consequence of an increased destruction of red cells. The administration of such substances as acetanilid, antifebrin and the nitrites is said to effect its formation in the circulating blood. It is also found in the urine and in the contents of cysts and old extravasates. It may be prepared by permitting blood or a solution of oxyhemoglobin to stand for a long time in the air, or by mixing a sample of blood with different oxidizing or reducing substances, such as ozone, potassium permanganate, ferricyanid or chlorate. Most observers agree that methemoglobin is a compound of hemoglobin with oxygen in which this gas is held in a different state of combustion. The compound is thereby rendered more stable, a change which is clearly betrayed by its greater resistance to vacuum. Not being able to unload its oxygen freely in the tissues, it is useless as a respiratory agent.

Methemoglobin exhibits a brownish tint and crystallizes in needles. Haldane suggests for oxyhemoglobin the formula: $\text{Hb} \begin{array}{c} \diagup \text{O} \\ | \\ \diagdown \end{array}$ and for methemoglobin, the for-

mula: $\text{Hb} \begin{array}{c} \diagup \text{O} \\ \parallel \\ \diagdown \end{array}$. The conversion of the former into the latter is not accomplished

directly by a mere shifting of the oxygen, but in an indirect manner, *i.e.*, by first dissolving all the oxygen and uniting any molecule of this gas that may be available, with the radicle.

Other Compounds of Hemoglobin.—If blood is freely exposed to carbon monoxid, a compound is formed between this gas and the hemoglobin which is known as carbon monoxid hemoglobin (CO—Hb).³ One molecule of the gas combines with one molecule of hemoglobin, thus effecting a very stable union which strongly resists the action

¹ Stokes's solution consists of:

Ferrous sulphate.....	2.0 per cent.
Tartaric acid.....	3.0 per cent.

When about to use this solution, add ammonium hydrate until the precipitate formed at first is redissolved.

² Discovered by Hoppe-Seyler, *Handb. d. physiol. chem. Analyse*, 1865, 205.

³ Attention was first called to this fact by Cl. Bernard, in 1857.

of the different reducing agents. Even air and pure oxygen are quite unable to destroy this combination with ease. For this reason, the inhalation of coal gas, or of illuminating gas of which carbon monoxid is a constituent, gives rise to symptoms of poisoning which are scarcely less severe than those following the abstraction of oxygen from the inspiratory air. Gradually, as the hemoglobin becomes more thoroughly charged with this gas, it fails in an increasing measure to bind the necessary amounts of oxygen. The tissues become oxygen-starved and eventually cease their normal activities. Death results, as a rule, before all the oxygen has been displaced. About one-fifth of its total amount most generally remains in the corpuscle. Carbon monoxid is also capable of uniting with the oxygen of the tissues, thereby destroying the life of the cells themselves.

Hemoglobin exhibits an avidity for carbon monoxid which is 140 times greater than that for oxygen. Thus, if the oxygen has been displaced by carbon monoxid, the hemoglobin cannot easily be made to recombine with the former. For this reason, the forcible introduction of air or pure oxygen into the lungs of an individual poisoned with coal gas or water gas, can have no other beneficial effect than the removal of that portion of the carbon monoxid which has as yet remained uncombined. To be sure, if a certain number of corpuscles are still present which have retained their normal capacity to carry oxygen, the metabolism of the tissues may continue at low ebb until more favorable conditions have been established in consequence of an active regeneration of the red cells. In severe cases, however, which necessitate a very quick production of new oxygen-carriers, large quantities of the carbon monoxid blood must be displaced by the process of blood-transfusion.

The blood of a person poisoned by carbon monoxid gas, possesses a cherry-red color. The muscles and organs, as well as the integument, exhibit a similar discoloration. The presence of very small quantities of this gas in the respiratory air ($\frac{1}{4000}$ – $\frac{1}{10,000}$) is sufficient to produce relatively large amounts of CO hemoglobin. It is for this reason that the admixture of even very slight quantities of this gas to the air of dwellings is so dangerous to life. It must be admitted, however, that some animals are more susceptible to it than others, which fact implies that the blood of animals differs somewhat in its power of absorbing this gas.

Illuminating gas contains another substance, ethylene, which seems to be strongly toxic to trees and seedlings. Its action upon animals is not known, but as it is highly toxic, even the slightest escape of illuminating gas should be carefully guarded against.

A compound of even greater stability results, if nitric oxid (NO) is brought into contact with hemoglobin. This union, however, cannot be effected in the body, because the oxygen which under normal conditions is always available, immediately instigates a reduction. For this reason, the formation of this compound necessitates the removal of the oxygen from the blood by hydrogen. Hydrocyanic acid (HCN) also enters into combination with hemoglobin, and it is also said that a typical sulfohemoglobin may be formed.

In accordance with the observations of Buckmaster and Gardner, showing that ether and chloroform lower the oxygen carrying power of the blood, it may be surmised that hemoglobin may also form a compound with these agents. This union is not identical with that ordinarily effected between these anesthetics and the lecithin or other lipins of the red corpuscles.

Derivative Compounds of Hemoglobin.—The decomposition of hemoglobin in the absence of oxygen gives rise to hemochromogen¹

¹ Discovered by Hoppe-Seyler, *Zeitschr. für physiol. Chemie*, xiii, 1889, 477.

and in the presence of this gas to hematin. Quite similarly, hematin may be reduced to hemochromogen, while the latter substance may be oxidized to hematin.

Hemochromogen is responsible for the color of hemoglobin and, therefore, of the blood. Solutions of this substance exhibit a cherry-red color. It may be prepared in crystalline form by mixing a drop of defibrinated blood with a drop of pyridin to which a small quantity of ammonium sulphid is then added. These crystals possess a stellate shape.¹

Hematin is an amorphous substance which may also appear as rhombic needles and platelets.² It possesses a dark-brown color, and while insoluble in water, alcohol and ether, is readily soluble in dilute alkalies and acids. It has lost the properties generally assigned to a proteid body and contains all the iron of the hemoglobin molecule. Its formula is given as $C_{32}H_{32}N_4FeO_4$. It is found in the

FIG. 104.—HEMIN CRYSTALS.

feces after the ingestion of meats and food rich in blood, as well as after hemorrhages into the stomach or intestinal canal. The reduction of the hemoglobin is accomplished in this case by the gastric and pancreatic juices.

A very important derivative of hematin is *hemin* or *chlorhematin*, the formula for which is given by Küster³ as: $C_{34}H_{33}O_4N_4FeCl$. One hydroxyl group of the hematin has been displaced by chlorin. This body is obtained in the form of crystals, the so-called Teichmann's hemincrystals. As these possess a very characteristic shape and color and may be derived from very small quantities of blood, the hemin reaction constitutes a most important test for blood. It is possible to prepare them in large numbers by carefully heating a droplet of blood which has been placed upon a glass slide. When dry, a drop or two of glacial acetic acid and a small crystal of sodium chlorid are added, after which a cover-slip is applied and the acid slowly evaporated by drawing the slide repeatedly through a flame. For purposes of examination, any dry stain which is suspected of being caused by blood, must first be thoroughly washed with small amounts of water and the water evaporated to dryness, while solid particles of blood should first be powdered with a few crystals of sodium chlorid.

¹ Donogamy, Jahresber. für Tierchemie, xxiii, 1894, 126.

² Piettra and Vila, Compt. rend., cxli, 1906.

³ Zeitschr. für physiol. Chemie, xl, 1904, 423.

On examining the slide under the microscope, the crystals are seen singly or in clusters. They appear as rhombic platelets and rods belonging to the monoclinic system. In transmitted light they possess a mahogany-brown color, while in direct illumination they exhibit a dark bluish tint. They are insoluble in water, alcohol, ether and chloroform, but soluble in dilute alkalis.

Hematoporphyrin differs from hemochromogen and hematin in that it contains no iron. Nencki¹ gives its composition as $C_{34}H_{38}N_4O_6 = 2C_{17}H_{19}N_2O_3$. It is prepared by adding crystallized hemin to a saturated solution of hydrobromic acid in glacial acetic acid. Having permitted this mixture to stand for three or four days, it is shaken with distilled water and filtered. The hematoporphyrin is then thrown down by carefully neutralizing with caustic soda. It is insoluble in water but soluble in acids, alkalis and ethyl alcohol. It appears as a dark, violet powder.

The fact that hematoporphyrin is free from iron is of general interest in so far as the bile pigments are also iron-free derivatives of hemoglobin; indeed, bilirubin and biliverdin are commonly regarded as excretory products derived from hemoglobin. The former pigment is isomeric with hematoporphyrin and both yield on oxidation acids which are identical with those obtained from hematin. In this connection, it should also be mentioned that the decomposition of stagnated blood, as for example that of hemorrhagic extravasations into the brain, gives rise to a red pigment, called hematoidin ($C_{32}H_{36}N_4O_6$) which is also free from iron and crystallizes in clinorhombic prisms. This body is said to be identical with the biliary pigment bilirubin and to be isomeric with hematoporphyrin. By abstracting one molecule of oxygen from the latter, a body, called mesoporphyrin, has recently been produced, which is said to possess the same composition as hematoidin. Traces of hematoporphyrin are generally present in the urine; greater amounts of it appear in certain types of poisoning. Crystals of hematoidin have also been found in the urine after transfusion of blood and during icterus, when there is a marked destruction of red cells. Of general interest is the fact that the green coloring matter of plants, known as chlorophyl, possesses a chemical structure similar to that of hemoglobin. It may be inferred, therefore, that these bodies are closely related to one another. This is shown, moreover, by the fact that hematoporphyrin may be reduced to the oxygen-free hemopyrrol which is methylprophylpyrrol. In a similar way, chlorophyl may be made to yield phylloporphyrin, a body closely allied to hematoporphyrin which in turn may be changed into hemopyrrol.²

CLINICAL METHODS FOR THE DETERMINATION OF HEMOGLOBIN

The hemoglobin content of the blood varies very slightly under normal conditions, but fluctuates considerably in disease. Two factors may be held responsible for this inconstancy, namely, a change in the number of the red cells or a change in their capacity to carry hemoglobin. While these changes may arise independently of one another, they are more frequently found to be associated with one another. In the second place, it should be remembered that they need not pursue a perfectly parallel course, because it frequently happens that a reduction in the hemoglobin content is associated with an increase in the number of the red cells. Conversely, a decrease in their number cannot justly be regarded as a certain indication of a loss in the total amount of hemoglobin, because the individual corpuscles may contain larger amounts of it.

¹ Monatshefte für Chemie, x, 1889, 568; and Zeitschr. für physiol. Chemie, xxx, 1900, 384.

² Nencki and Marchlewski, Ber. der chem. Gesellsch., xxxiv, 1901.

As a disturbance in the relationship of these two factors is most likely to result in consequence of pathological conditions, it is essential to be in possession of a quick and accurate method for the quantitative determination of this substance. It is quite true that a knowledge of the hemoglobin content of the blood frequently facilitates the diagnosis, but, as has just been emphasized, this value must first be brought into relation with the number of the red cells, otherwise it may give rise to very erroneous deductions regarding the general condition of the blood. Two methods have been advocated for the determination of hemoglobin. One of these has been described by Welker and Hoppe-Seyler,¹ and is known as the chronometric. The other, described by Vierordt and Glan,² is known as the spectrophotometric. The various modifications of the first take the normal quantity of hemoglobin to be 100 per cent. and the normal number of the red corpuscles (5,000,000 per cu. mm.) also 100 per cent. The color exhibited by a sample of blood of this quality is regarded as unity; this standard being obtained by employing the percentage of hemoglobin as the numerator and the percentage of the corpuscles as the denominator. Thus, if the number of the red cells remains the same, while their hemoglobin content is diminished, the color index becomes smaller than 1. A reduction of the hemoglobin to 80 per cent. gives an index of $\frac{80}{100} = 0.8$, which value implies that the different corpuscles carry only $\frac{8}{10}$ of the normal quantity of hemoglobin. Under certain pathological conditions the decrease in the percentage of hemoglobin is often associated with a diminution in the percentage of the corpuscles; moreover, the reductions may or may not be equally great in the two cases. If they are equal, the color index is 1, and if they are not, the latter is either smaller or larger than 1. To illustrate, assuming that the percentage of hemoglobin is 60 and the percentage of corpuscles 80, the index: $\frac{60}{80} = 0.75$, suggests that the different corpuscles are loaded with only three-fourths of the amount of hemoglobin ordinarily carried by them. And again, a percentage of hemoglobin of 60 and a percentage of red cells of 50 gives the index: $\frac{60}{50} = 1.2$, which indicates that the hemoglobin content of the individual corpuscles is greater than normal.

The principle involved in this method is the following: If two solutions in identical receptacles are exposed to the same source of light and exhibit the same color, their content in coloring matter must be the same. Hence, it should be possible to prepare a solution of hemoglobin of known concentration and to determine the hemoglobin content of other samples of blood by simply comparing them with this standard solution. But, as standard solutions of this kind cannot always be easily kept, the attempt was made at an early date to find a more permanent

¹ Zeitschr. für physiol. Chemie, xv, xvi, xxi, 1891, 1892, and 1896.

² Poggend. Ann., 1877.

colometric substitute; for example, solutions of the more stable compounds of hemoglobin, solutions of picrocarmin and colored glass.

The instruments which have been devised to permit of a comparison of this kind are called *hemoglobinometers*, or *hemometers*. Hoppe-Seyler employed two glass troughs with parallel sides, into one of which he placed a standard solution of oxyhemoglobin of known strength, and in the other, the blood to be tested. The procedure consisted in diluting the sample of blood until its color corresponded precisely with that of the standard solution. The quantity of water necessary to attain this end, enables one to calculate the proportion of hemoglobin in the undiluted blood. The procedure advocated by Tallqvist,¹ consists in permitting a drop of blood to fall upon white filter paper. When evenly diffused the color of the stain is compared with similar permanent stains indicating the different percentages of hemoglobin from 10 to 100. The *hemophotographic method of Gärtner*² is based upon the fact that a solution of oxyhemoglobin absorbs the rays of light in a steadily increasing measure with its concentration. *Fleischl's instrument*³ consists of a short cylindrical receptacle which is divided into two compartments by a vertical median partition. Into one of these is placed a measured

FIG. 105.—HEMOGLOBINOMETER. (Fleischl's.)

S, stage; R, reflecting mirror; B, screw for adjusting position of colorimetric wedge; A, the cylindrical receptacle. C, contains two compartments into one of which is placed the sample of blood to be examined.

FIG. 106.—HEMOGLOBINOMETER. (Gowers.)

A, tube filled with colored fluid; B, tube for mixing blood; C, receptacle for distilled water with dropper; D, pipet.

¹ Berliner klin. Wochenschr., 1904.

² Münchener med. Wochenschr., 1901.

³ Wiener med. Jahresb., 1885; modified by Miescher, Korresp. f. Schweizer Ärzte, xxiii, 1893.

quantity of the blood to be tested plus a definite amount of water. A glass wedge is situated beneath the other compartment, stained in different reds to correspond to the color of different solutions of hemoglobin of known concentration. This scale is then moved onward until its color corresponds precisely with that of the sample of blood. Thus, if the colors are matched, say, at division 75 of the scale, the blood contains only 75 per cent. of the normal quantity of hemoglobin. Miescher has endeavored to obviate the use of solutions and has succeeded in producing an instrument of even greater precision than that of Fleischl. *Gower's hemoglobinometer*¹ which is the one most commonly employed to-day, consists of two identical glass tubes, *A* and *B* (Fig. 106). Tube *A* is filled with glycerin-jelly to which picrocarmin has been added until its color corresponds precisely to that of a 1 per cent. solution of hemoglobin, i.e., to that of normal blood diluted 100 times. Tube *B* is filled with 20 cu. mm. of blood to which a few drops of distilled water have been added to prevent coagulation. Water is then dropped into this receptacle by means of a pipet until the color of the diluted blood corresponds precisely with that of the standard solution in tube *A*. The gradations upon tube *B* accurately represent the percentage of hemoglobin. It is necessary to transpose the tubes repeatedly. Thus, if the original 20 cu. mm. of blood are matched at division 80, the blood contains but 80 per cent. of its normal amount of hemoglobin. The following modification of this method has been suggested by Haldane.² In tube *A* is placed a 1 per cent. solution of blood saturated with carbon monoxid. Having dropped 20 cu. mm. of blood plus a slight amount of distilled water into tube *B*, the hemoglobin contained in it is quickly converted into carbon monoxid hemoglobin by charging it with pure carbon monoxid or by passing a mixture containing this gas through it. The dilution of the sample of blood is then accomplished in the manner described previously. Sahli³ employs a solution of hematin chlorid and first converts the blood to be tested into hematin chlorid.

SPECTROSCOPIC ANALYSIS OF HEMOGLOBIN AND ITS DERIVATIVE COMPOUNDS

The most essential part of the spectroscope is a glass prism *P*, which receives a bundle of white light through tube *A* (Fig. 107). The size of this bundle may be varied by altering the size of the slit-like opening in the end of this tube, while a biconvex lens interposed in this place serves to render the rays parallel and to concentrate them upon the surface of the prism at *C*. The spectral components of the white light are observed in magnified form through tube *B* which is nothing more than a small telescope. The third tube *D* contains a scala *M* which is illuminated and reflected upon the surface of the prism at *C*. In this way, the spectral colors (red to violet) may be observed in conjunction with the divisions of the scala.

If a colored medium, for example, a solution of hemoglobin is now placed between the source of light and the opening in tube *A*, some of the rays of white light are prevented from entering, i.e., they are absorbed. In consequence of this absorption, certain sections of the spectrum as observed through tube *B*, appear in different shades of black. These dark bands situated in between the different colors, are commonly called absorption bands. Of greatest importance, however, is

¹ The Lancet, 1878.

² Jour. of Physiol., xxvi, 1901, 497.

³ Lehrbuch der klin. Untersuchungsmeth., 1905.

the fact that different substances affect the spectrum in very specific ways so that it is possible to determine their presence by the number, intensity and location of the absorption bands. But, as some of these bands occupy the same or very nearly the same positions, it is desirable to possess certain landmarks in the spectrum for our guidance. This purpose is served by the Fraunhofer lines. The spectrum of sunlight extends between the ultra red and ultra violet colors, *i.e.*, between rays possessing, on the one hand, a wave length of $757\mu\mu$,¹ and, on the other, one of $392\mu\mu$. The Fraunhofer lines traverse the spectrum at definite distances from one another. Thus, the *B*-line transects the red end with a wave length of $686.8\mu\mu$, the *D*-line the golden yellow with a length of $589\mu\mu$, and the *E*-line the green with a length of vibration of $527\mu\mu$.

FIG. 107.—DIAGRAM OF SPECTROSCOPE.

The spectrum of oxyhemoglobin is a very characteristic one. Two absorption bands are visible at the border of yellow and green, between the Fraunhofer *D*- and *E*-lines (Fig. 108). The left band is narrow but dark and sharp and is generally designated as the " α -band." The one on the right, which is broad and less clearly outlined, is referred to as the " β -band." But as the absorption of the light is dependent upon the thickness and the concentration of the solution, these bands are not always equally distinct. Thus, if the percentage of oxyhemoglobin is greater than 0.65, the bands coalesce and the yellow-green color between them disappears. Greater concentrations eventually give rise to one dark band which overlaps the *D*- and *E*-lines and causes a darkening of the violet end of the spectrum. Quite similarly, very dilute solutions (0.01–0.003 per cent.) produce only a single band, namely, the one nearest the *D*-line. It is essential, therefore, to employ solely solutions in strengths of from 0.1 to 0.6 per cent., while the layer of the solution should be 1 cm. in thickness. These bands may also be obtained from circulating arterial blood. A good object for this purpose is the ear of the rabbit, a hand spectroscope being applied directly to its surface.

Reduced hemoglobin gives only one absorption band which is commonly spoken of as the " γ -band." It is situated between the *D*- and *E*-lines, extending farther toward the red end of the spectrum and slightly beyond the *D*-line. It exhibits a considerable width and rather poorly defined margins, but its characteristics vary somewhat with the strength of the solution.

The spectrum of hemoglobin and its oxygen combination is invariably made use of in the detection of blood, the suspected substance, smear or stain being first extracted with a definite quantity of normal saline solution. In these examinations

¹ $1\mu\mu$ = 1 millionth of a millimeter.

the attempt must also be made to convert the oxyhemoglobin into hemoglobin and the latter into the former. Thus, if a certain solution yields the α - and β -bands, a reducing agent should be added to obtain the γ -band, because this conversion establishes the presence of blood with much greater certainty than the presence of the first two bands alone. Quite similarly, a solution in which hemoglobin has been proved to exist spectroscopically, should be oxidized by shaking it until the γ -band is eventually displaced by the two bands of oxyhemoglobin.

Solutions of carbon monoxid hemoglobin also give two absorption bands which may be mistaken at times for those produced by oxyhemoglobin; however, a differentiation is readily possible if the solutions are properly diluted. When this has been done, the superposition of the different spectra so far described, will show that the bands of carbon monoxid hemoglobin are situated somewhat nearer the blue end of the spectrum; and besides, they are permanent in character, *i.e.*, they cannot be fused into a single one by the addition of a reducing agent.

FIG. 108.—The spectra of oxyhemoglobin in different grades of concentration, of reduced hemoglobin, and of carbonic oxid hemoglobin. (After Preyer and Ganger.) 1 to 4. Solution of oxyhemoglobin containing: (1) less than .01 per cent., (2) .09 per cent., (3) .37 per cent., (4) .8 per cent. 5. Solution of (reduced) hemoglobin containing about .2 per cent. 6. Solution of carbonic oxid hemoglobin. In each case of the six cases the layer brought before the spectroscope was 1 cm. in thickness. The letters indicate Fraunhofer lines and the figures wave-lengths expressed in $\frac{1}{100,000}$ millimeter.

Nitric oxid hemoglobin shows two absorption bands which are paler and less distinct than those of carbon monoxid hemoglobin and furthermore, their characteristics cannot be altered by reducing agents.

The absorption bands of methemoglobin in watery or acidified solutions are very similar to those of acid hematin, which body gives three to four distinct bands. A differentiation, however, can easily be effected, because methemoglobin when mixed with a small quantity of an alkali and a reducing agent, shows the absorption band of reduced hemoglobin, while under precisely the same conditions hematin exhibits the spectrum of an alkaline hemochromogen solution. In alkaline solutions this substance shows three bands, two of which are similar to those of hemoglobin. They differ from the latter in that the β -band is more conspicuous than the α -band; moreover, the latter occurs in relation with a third band which is fainter and occupies a position somewhat to the left of the *D*-line.

Hemochromogen in acid solution has four bands and, in alkaline solution, two bands. One of the latter is dark and is situated between the *D*- and *E*-lines, while the other is less intense and covers the *E*-line.

Acid hematin possesses a sharply defined absorption band between the *C*- and *D*-lines, the position of which varies somewhat with the type of the solution employed. A second band, much broader but less intense, is present between the *D*- and *F*-lines. By proper dilution this band may be converted into two. The one nearest the *F*-line is dark and broad, and the one nearest *E*, light and narrow. Another very faint band may be made out near *D* by diluting the liquid still further. Hematin in alkaline solution presents one broad absorption band located principally between the *C*- and *D*-lines, but extending slightly into the space to the right of *D*.

On addition of a few drops of hydrochloric acid, an alcoholic solution of **hematophorphyrin** presents two bands, namely, one near *D* which is narrow and faint, and one between *D* and *E* which is broad and sharply outlined. A dilute alkaline solution of this substance presents four bands, namely, one between *C* and *D*, one between *D* and *E* and covering *D*, one between *D* and *E* and very close to *E* and lastly, one near *F*. With the aid of an alkaline zinc chlorid solution these bands may be made to coalesce into two, namely, into one located at *D* and one situated between *D* and *E*. In acid solutions this substance frequently shows four bands, but much depends upon the manner in which the solution is prepared.

THE LIFE HISTORY OF THE RED CORPUSCLES

In the embryo the red cells originate in the so-called vascular area. The blood-vessels appear at this time as a network of solid threads, differentiated from the adjoining tissue by a greater opacity. Their walls are made up of masses of cells which are intermingled with ameboid corpuscles and of cells which possess a peculiar branched appearance. Later on, when fluid has forced its way into the different tubules from without, the cells on the outside arrange themselves in the form of an endothelial lining, while loose clusters of large globular cells project from here into the lumen of the vessel. All these cells multiply very rapidly by indirect division. The cytoplasm of those fastened to the inside wall is colorless and nucleated at first, but gradually acquires a certain quantity of hemoglobin. These cells become yellowish in color and eventually separate to assume a position in the fluid within the channel. Being still in possession of a nucleus, they are capable of multiplying by indirect division. Later on, however, as the individual tubules acquire a larger size and begin to anastomose with one another, these newly developed cells, in which we recognize the red corpuscles, migrate into the general circuit and henceforth lead an independent life.

During the later stages of embryonic development, other organs enter into the formation of these elements. To begin with, this function is centralized in the liver; subsequently, however, the spleen, lymphatic tissues and red marrow of the bones take part in their production. During the last periods of embryonic existence the importance of the liver and spleen as corpuscle-forming organs decreases very markedly, while that of the bone marrow increases steadily until the end of fetal life.

During the early stages of embryonic existence, the precursors of the red corpuscles, generally known as **erythroblasts**, are large and nucleated, while the non-nucleated cells which are so characteristic of the adult animal, appear at a much later time. In the human fetus, for example, all the cells are nucleated at the end of the fourth week, while at the end of the third month only about one-fourth of their total number is still in possession of a nucleus. The corpuscles of the latter type become fewer and fewer in number as gestation advances until at birth practically all the circulating erythrocytes are without a nucleus. Only those which are still retained in the corpuscle-forming, or *hematopoietic tissues*, remain nucleated. Naturally, the loss of the nucleus which occurs either by disintegration or extrusion, implies that they are now fully developed and also, that they no longer multiply by simple division.

The formation of the red corpuscles does not cease at the end of intrauterine existence, but is continued throughout the life of the animal; and furthermore, as their number does not increase, their formation must be counterbalanced by an adequate destruction. That this is true may be inferred from many experiments. Thus, if a loss of red corpuscles is effected by bleeding, the fluid parts of the blood are quickly replaced by transferring a certain quantity of the tissue-lymph into the vascular system. Consequently, the blood is relatively poor in corpuscles directly after the hemorrhage, but acquires them in greater numbers later on as new ones are sent in by the hematopoietic tissues. An interval of a few days generally suffices to establish the normal corpuscle count, but naturally, much depends upon the quantity of blood lost and the activity of the corpuscle-forming tissues. A second fact that should be mentioned at this time is the constant outgo of pigmentous material in the feces and urine, in the form of urochrome, urobilin and stereobilin. It has been shown that these substances originate in the liver and that their production is closely dependent upon the amount of hemoglobin available for this purpose. By inference, therefore, it may be concluded that a supply of this coloring material must be constantly at hand; *i.e.*, it must be brought to this organ by the red cells in undiminishing quantities.

During extrauterine life the erythrocytes are formed in the red marrow of the bones. Marrow of this color is found in the flat and short bones of the head and trunk and in the long bones of the extremities. The latter, however, contain it solely in their ends. It is also to be noted that the yellow marrow in the other regions of these bones may assume the characteristics of red marrow at any time when a very active regeneration of the red cells is called for. The fatty marrow in the diaphyses then becomes filled with a red pasty mass consisting chiefly of red cells and their precursors. This conversion may readily be induced in animals by bleeding. A similar change has been observed in hibernating animals. Red marrow is formed very

rapidly in the spring, while, at the beginning of the period of hibernation, the yellow marrow is present in especially large amounts.¹ In the frog, lymphoid red marrow appears only in the early summer, which fact indicates that this animal obtains a considerable supply of new red cells at this time of the year.²

The precursors of the red cells are called erythroblasts, while the process by means of which these cells are converted into mature red corpuscles, is known as *hematopoiesis*. Their migration into the blood-stream is greatly facilitated by the circulatory conditions existing in the marrow. In the first place, it is to be noted that these channels are protected by unyielding bony walls, while their cellular lining is thin and rather imperfect. And besides, as the rapidity of the blood flow is slight and the pressure low, a certain traction is brought to bear upon them, but naturally, the quickness with which they are formed and are forced into the circulation, depends in a large measure upon how greatly the system is in need of them. Thus, it is possible to retard the production of these elements in such a degree that the lumen of the vessels becomes practically free from them, while the region close to their wall is filled with cells in all intermediary stages of development. It is also possible to stimulate the hematopoietic process by causing a greater destruction of the circulating red cells. This end may be attained either by bleeding, or by the administration of toxic substances. The histological picture then obtained is quite different from that just given, because the lumen of the channel is now filled with young erythrocytes, many of which are still in possession of a nucleus. Some of these nucleated cells find their way into the general circulation, where they are recognized as *normoblasts*. Under certain pathological conditions the liver and the spleen seem to regain the corpuscle-forming power which they possessed during embryonic life.

While the duration of the life of the red cells has been estimated at about four weeks, it cannot be said that this point has been definitely settled. The attempt has been made to arrive at a conclusion by introducing a limited number of elliptical corpuscles into the circulation of a mammal. It seems, however, that the length of time during which the cells of the lower forms or of birds continue to live in the mammalian blood, cannot be regarded as a safe guide, because as they are thus placed into a medium which is foreign to them, they may go to pieces much sooner than they would otherwise. Another method to which brief reference should be made here, depends upon the determination of the number of red cells which must be destroyed daily in order to permit of the excretion of the usual amounts of bile pigment. If the quantity of bile is 15 grams per kilo of the body weight and the percentage of its pigment 0.2, the daily output of pigment must amount to 1.95 grams. But in order to obtain this quantity of

¹ Pappenheim, *Zeitschr. für klin. Med.*, xliii, 1901, 363.

² Marquis, *Dissertation*, Dorpat, 1892.

pigment, 48 grams of hemoglobin must be made available, *i.e.*, about one-tenth of the total amount of this substance ordinarily present in an individual weighing 65 kilos and possessing about 3500 grams of blood. Upon the basis of this calculation, the life of the circulating red corpuscle may be said to be about ten days. Our long cherished beliefs regarding the production of bile pigments, however, do not agree with the views of Hooper and Whipple,¹ because it seems that the liver possesses a certain inherent power to form pigment, thus quite offsetting the calculation just given. A relatively severe loss of red corpuscles, which must be compensated for immediately, occurs during the menstrual flow. Mix² states that 150 c.c. of blood are lost during this period which are again reformed in the course of about twenty-eight days. This necessitates the formation of 5000 cu. mm. of blood in a day, 208 cu. mm. in an hour or 3.5 cu. mm. in a minute. The total number of red corpuscles lost during this period, necessitates the formation of 15,750,000 new cells in a minute.

It seems that the disintegration of the red cells begins while they traverse the general circulatory channels, but their absolute destruction and dissolution is restricted to two organs, namely, to the liver and the spleen. Moreover, it is very probable that the former organ possesses a much greater disintegrating power than the latter, which belief may be substantiated by the following facts:

(a) The liver is the place in which the hematin is changed into bile pigment, and hence, an adequate supply of the former substance must always be kept on hand.

(b) The hepatic cells contain iron which is normally derived from the red corpuscles. This fact may be established by treating a cross-section of this organ with potassium ferrocyanid and acid alcohol, under which condition it assumes a blue color. While a part of the iron is excreted, a part of it is reabsorbed and may again be employed in the formation of new corpuscles.

(c) The quantity of the biliary pigment may be increased by injecting hemoglobin into the blood stream.

(d) The deposition of iron in the liver may be increased experimentally by inciting a greater destruction of the red cells. This can be done by introducing toxic agents into the circulation. A disintegration of red cells also occurs under pathological conditions, for example, in the course of certain anemias.

(e) A deposition of hemoglobin crystals in the cells of this organ has been observed.

(f) The blood of the hepatic vein is said to contain fewer red cells than that of the portal vein.

(g) The endothelial cells lining the capillaries of the liver, the so-called "Sternzellen," possess the power of taking up foreign particles and of rendering the red corpuscles effete.

A disintegration of the red corpuscles also occurs in the lymphoid tissues and in the spleen. This conclusion is based upon the observation that red cells or pieces of them are found at times in the cytoplasm of certain large cells, or macrophages, which are generally present in

¹ Am. Jour. of Physiol., xlii, 1917, 256.

² Boston Med. and Surg. Journal, 1892.

these organs. It seems best, however, not to attach too great an importance to this fact, because it can readily be shown that the spleen is neither the only nor the most important organ for the destruction of these elements. The evidence which tends to confirm this statement is as follows:

(a) The removal of the spleen does not seem to lessen the destruction of the red cells, as is evinced by the quantity of the bile-pigment excreted.

(b) If a marked destruction of red corpuscles actually did occur in the spleen, the phagocytic cells of this organ should be loaded to their utmost capacity with these cells or with the substances derived from them. This histological evidence has not been supplied as yet.

(c) Quite similarly, the blood emerging from this organ should show a corpuscle count below that of the arterial blood, and, furthermore, should also contain those bodies which are ordinarily derived from the red corpuscles. That the splenic blood undergoes these changes has not been definitely established.

CHAPTER XVII

THE WHITE BLOOD CORPUSCLES

PHYSICAL AND CHEMICAL PROPERTIES

Color, Shape and Size.—The white corpuscles appear as small globules of protoplasm, measuring from 4 to 14 μ in diameter. Some of them, therefore, are much larger and some much smaller than the red cells. Their substance is soft and sticky, grayish in color, homogeneous or granular, and not surrounded by a clearly recognizable membrane. Their surface is often quite uneven and shows at times irregular projections which break off and float free in the blood. Although these cells are strongly refracting, their nuclear portion does not become sharply differentiated until they have been brought in contact either with suitable stains or with water and solutions of acetic acid. These agents serve to contrast them more sharply against the medium, because water tends to render the granules more conspicuous, while acetic acid lessens the opacity of their cytoplasm.

The Classification of the White Corpuscles.—The white cells may be arranged in groups in accordance with the shape and size of their cell-bodies and nuclei, as well as in accordance with certain differences in the behavior of their granular constituents toward anilin dyes. Ehrlich¹ found that some of these granules react only toward acid dyes, while others can only be stained with basic or neutral pigments. For this reason, the white corpuscles have been described as acidophiles,² basophiles and neutrophiles. In accordance with their general characteristics, they are divided into two principal groups and these again into several others, as follows:

¹ Archiv f. (Anat. u.) Physiol., 1879, 571, and "Die Anemie," 1898.

² Also called oxiphiles or eosinophiles.

1. *Lymphocytes*, are not granular¹ and do not show a very pronounced shifting of their substance.

(a) *Small Type*.—These cells possess a small amount of cytoplasm and a relatively large and symmetrical nucleus. They are about as large as the red corpuscles and constitute about 25 per cent. of all the white corpuscles.

(b) *Large Type*.—These cells are much larger than the preceding and display a broader margin of cytoplasm around a somewhat eccentric nucleus. They are few in number and often exhibit a granular, irregularly stained network simulating true granulations.

2. *Leukocytes*, are granular and exhibit a very characteristic ameboid motion.

(a) *Transitional Type*.—These cells are few in number (2 to 10 per cent.) and contain a large quantity of protoplasm in which a few neutrophilic granules are suspended. The nucleus is shaped like a horseshoe or an hour-glass, but is not divided into smaller masses.

FIG. 109.—DIFFERENT VARIETIES OF HUMAN WHITE CORPUSCLES.

A, lymphocyte; B, mononuclear leukocyte; C, transitional form; D, polynuclear leukocyte; E, eosinophile leukocyte; F, mast-cell. (After Szymonowicz.)

(b) *Polymorphonuclear Type*.—The protoplasm of these cells is abundant and embraces many fine *neutrophile* granules. The nucleus is lobulated, its different segments being connected by strands. They form about 70 per cent. of the total number of the leukocytes. To this group also belong the *eosinophilic leukocytes* which, as the name indicates, stain with acid dyes, such as eosin. They are characterized by their coarse and strongly refracting granules, and show a most active ameboid motion.

(c) *Basophile Type*.—These cells are frequently called mast-cells.² They are present in small numbers under normal conditions (less than 1 per cent.) and embrace a nucleus consisting of two or three segments. Their granules stain deeply with basic dyes, such as thionin.

The Number of the White Corpuscles.—It is generally given as 6000 to 10,000 per cu. mm., which figure indicates a proportion of one white to about 700 red corpuscles. The total number of white cor-

¹ True granules are present in severe anemias, but rarely in health.

² Discovered by Donders and Molischott in 1848; also see: Hirt, Dissertation, Leipzig, 1855.

puscles has been estimated at 19–32,000,000,000. They are especially numerous in the new-born, counts of 15,000–19,000 per cu. mm. being not infrequent. They become fewer in number shortly after birth, but again increase during infancy, when a value of 30,000 per cu. mm. cannot be regarded as abnormal. From the first to the sixth year the values range between 13,000 and 7000 per cu. mm. A second decrease takes place in adult life. This is again followed by an increase in old age. The ingestion of food rich in protein raises the count, but maximal values are not obtained until two or three hours after meals. Very pronounced increases of this character constitute the so-called assimilation or digestion leukocytosis. Fasting lowers the count, while muscular activity¹ and massage² raise it.

A transitory increase above the physiological maximal value is designated as leukocytosis, while a reduction below the minimal value is called hypoleukocytosis or leukopenia. In accordance with the data given above, it is advisable to classify leukocytosis as physiological and pathological, this division being based solely upon the cause of the increase. A pathological leukocytosis, for example, arises in the course of many febrile reactions and especially after hemorrhages and in consequence of suppurative processes. It is also possible to produce this condition by the administration of quinin, turpentine, albumose, nucleic acid, bacterial products and extracts of thymus, spleen and bone-marrow. A leukopenia of marked degree frequently follows exposure to the Röntgen rays.

The method employed in determining the number of the leukocytes is the same as that made use of in counting the red cells, but as a larger drop of blood is needed in this case, the pipet and counting chamber must be somewhat larger in size.³ In order to render the white corpuscles more conspicuous, the red corpuscles must first be destroyed by adding a small quantity of acetic acid to the diluting fluid. It is also possible to add some coloring material to the latter so that the total count may at the same time be amplified by a differential count.⁴ In general, however, it is advisable to differentiate these cells in a stained smear, because abnormal forms of leukocytes are difficult to recognize in the counting chamber.

The Chemical Composition of the White Corpuscles.—The direct chemical analysis of the white corpuscles meets with the difficulty that it is quite impossible to secure these cells in sufficient numbers. Their chemical characteristics, however, have been studied in an indirect way by making use of the so-called pus-corpuscles which are always present in tissues which have been invaded by pus-producing

¹ Zuntz, *Physiologie des Menschen*, Berlin, 1901.

² Zangemeister and Wagner, *Deutsche med. Wochenschr.*, xxviii, 1902, 549.

³ A special counting cell has been devised by Brener (*Berliner klin. Wochenschr.*, xxxix, 1902, 954).

⁴ Türk (*Wiener klin. Wochenschr.*, xv, 1902, 715) recommends a mixture of:

Glacial acetic acid.....	3 c.c.
Distilled water.....	300 c.c.
Gentian violet, 1 per cent. aqueous solution.....	2 to 3 c.c.

Also see: Zollikofer, *Zeitschr. f. wissenschaft. Mikr.*, xvii, 1900, 313.

bacteria. It is also possible to obtain large numbers of lymphocytes from lymphatic glands. As will be explained more fully later on, the pus-corpuscles are the remnants of destroyed leukocytes. They show a content in water of 90 per cent. The solids (10 per cent.) consist chiefly of albumin, globulin, nuclein, nucleoproteid and nucleohiston. Neutral fats appear in their cytoplasm as strongly refracting granules. Cholesterin, lecithin, glycogen and alkaline phosphates are also present.

The Origin and Fate of the White Blood Corpuscles.—The different views regarding the formation of the white corpuscles may be said to advocate either a *monophyletic* or a *dualistic* origin. In accordance with the former, the different varieties of white corpuscles are regarded as having arisen from a single mother-cell.¹ To be sure, the facts favoring this unitarian mode of generation are insufficient, at least when applied to the adult animal, but it is also true that the objections commonly raised against it, lose much of their weight when the conditions existing in the embryo are more fully considered. The dualistic theory is based upon the contention that the lymphocytic white cells arise from the so-called lymphoblasts which are present in the adenoid tissue of the lymphatic glands and lymph nodules, and that the larger ameboid types, or leukocytes, are descended from the myeloblasts of the bone-marrow. This view, which was first expressed by Ehrlich, is the most favored at the present time.

The lymph nodule consists of a dark peripheral and a clear inner zone, or germ center. The latter is formed by large cells which divide and give rise to the lymphocytes. The largest number of these then escape into the lymph channel situated at the periphery of the nodule, but a few of them also enter the blood stream directly. Those white corpuscles which originate in the marrow of the bones, have as their precursors the so-called myelocytes which present themselves as granular or non-granular protoplasmic masses with rounded nuclei. By transition these elements finally assume the characteristics of the leukocytes, and eventually escape into the blood capillaries of the marrow, whence they are distributed to all parts of the body.

The duration of the life of these colorless corpuscles has not been determined with accuracy. They undergo dissolution and disappear. Many of them are destroyed while engaged upon their mission of ridding the body of toxic substances.

THE FUNCTION OF THE WHITE BLOOD CORPUSCLES

Contractility and Motion.—A molecular movement of the cytoplasm has been observed in all white corpuscles, but with the exception of the polynuclear and mononuclear varieties, this movement is not sufficiently strong to cause motion. White cells may be obtained without much difficulty by placing a drop of blood upon a glass slide

¹ Weidenreich, *Ergebn. der Anat. und Entwicklungsgeschichte*, xix, 1911, 2.

and removing from it the red corpuscles by means of a lateral drainage stream of slight force. The white cells then stick to the surface of the slide and, if kept in a warm isotonic solution, may be studied for some time thereafter. They may also be obtained from the frog by inserting a platelet of porous wood under the skin covering the dorsal aspect of its body. If permitted to remain in this position for several hours, the meshes of the wood will be filled with many leukocytes, the removal of which can easily be effected by washings with normal saline solution. They may be studied in a more plastic manner by placing the frog's mesentery or bladder under the microscope. In the circulating blood they appear as translucent globular bodies, which, on account of their lesser specific gravity, leave the swift axial stream and enter the more slowly moving peripheral layers of the current. They attach themselves here or there to the vessel wall, but soon pass onward again by executing a peculiar rotary motion.

Under favorable conditions the leukocytes exhibit a movement of their cytoplasm¹ which is very similar to that displayed by the ameba. Their substance contracts and relaxes alternately, while their nuclear constituents remain rather stationary and serve, so to speak, as a center for this movement. Prolongations, commonly designated as pseudopodia, are sent out in different directions into the surrounding medium to be again retracted later on with varying swiftness.² Thus, a leukocyte may extend and retract its pseudopodia repeatedly without altering its position, but it may also happen that one of its prolongations becomes attached to the surface and that the remaining mass of the cell is slowly moved onward in the direction of this fixed point. This property of the leukocytes to adhere to surfaces is attributed by Verworn to the extrusion of a mucous secretion. When freely moving they usually present a globular outline which implies that they are in a state of contraction.

Phagocytosis.—Whether the leukocyte remains stationary or moves onward to a different place, the molecular shifting of its substance is instrumental in bringing it into relation with various particles of food and other extraneous material. As is true of other low forms of life, the leukocyte behaves in a very characteristic manner toward these substances, being either attracted or repelled by them. This orientation is brought about largely by chemical means, and hence, the leukocytes may be said to possess the property of chemotropism or chemotaxis of a positive and negative kind.

The chemotropic qualities of the leukocytes must be held responsible for their power of taking up nutritive particles and of englobing and digesting all that material which is foreign or injurious to the body.

¹ First observed by Wharton Jones in 1846, and proved for the human leukocyte by Davaine in 1850. Lieberkühn gave an adequate description of this movement in 1854.

² Verworn, Pflüger's Archiv, li, 1891; also see: Maximow, Ziegler's Beiträge, lxxiii, 1909 and lxxvi, 1910.

For this reason, they are frequently spoken of as devouring cells or phagocytes (to eat-cell), and are further characterized as the "police-men of the blood." In illustration of their function the following phenomenon may be cited: As the larva of the fly changes into the mature insect—a metamorphosis which occurs rather rapidly—such structures as the creeping muscles become superfluous and undergo degenerative changes. The substances which are formed during this catabolic process, exert a strong chemotactic influence upon the leukocytes with the result that this tissue soon becomes overcrowded with them. The ensuing phagocytosis soon leads to the removal of these now useless parts. The absorption of the tail of the tadpole is accomplished in a similar manner. It is also known that they invade injured tissues and help in the removal of the superfluous cellular material, but whether they actually take part in the process of reconstruction, is still doubtful. To be sure, Metchnikoff¹ has expressed

FIG. 110.—LEUKOCYTES ENGULFING PARTICLES OF INDIA INK.

the idea that the emigrated leukocytes undergo certain changes which enable them to become connective-tissue cells, but most authors believe that this regeneration is accomplished solely by the plasma cells of the tissues.

Of even greater importance and interest are the phagocytic qualities displayed by the leukocytes when brought in relation with pathogenic bacteria. But while capable of ridding the body of different dead and living germs, the leukocytes are not capable of destroying all varieties of them. They seem to be attracted especially by the ordinary pus microbes or by the products of their metabolism, which fact is well proven by an experiment described by Pfeiffer. A capillary tube, closed at one end, is filled with a culture of staphylococcus pyogenes albus or aureus. It is then placed under the skin or into the abdominal cavity of a rabbit. On removing it 10 to 12 hours later, the microscopical examination reveals great numbers of leukocytes in the culture, actively engaged in ingesting the bacteria. The fact that the bacteria, and not the culture, are responsible for the migration of the leukocytes into the tube, can readily be proven by employing a

¹ *Pathol. compar. de l'inflammation*, Paris, 1892.

medium containing no germs. Under this condition the leukocytes do not enter the tube.

Opsonins.—It was observed at an early date that the leukocytes behave at times in a very indifferent manner toward certain types of bacteria, and hence, it was thought likely that these germs must first be killed before the phagocytosis can take its regular course. Metchnikoff then expressed the view that the leukocytes are capable of surrounding living material under ordinary conditions, but that the complete destruction of the latter necessitates the presence of a specific intermediary agent. It was assumed, therefore, that the fluids of the body contain special activators which stimulate the leukocytes to greater activity.

Leishman¹ and Wright and Douglass² showed later on that the phagocytosis may be greatly augmented by blood plasma or serum which has been treated in a particular way. It could be proved by the centrifugalization of bacterial mixtures that this process tends to diminish the reinforcing power of the serum, while the bacteria are "sensitized thereby," *i.e.*, they are rendered especially vulnerable to the leukocytes. In this way, it has been established that the bacteria interact with certain specific bodies of the blood. These bodies which, so to speak, render the bacteria palatable to the leukocytes, are called opsonins (prepare for a meal).

The function of the opsonins, therefore, is to produce certain physicochemical changes in the substance of the bacteria so that the leukocytic material is able to react with it. Paint applied to window glass will soon crumble off, but will stick to it for an indefinite period if the glass is first eroded with a fluoride. The opsonins are comparable to the eroding fluid. They attack the bacterial substance and lessen its power of resistance so that the leukocytic material is able to combine with it.

The resistance and immunity of an animal against microbic infections depends in a measure upon the phagocytic properties of its leukocytes. But in order to attain this power it is necessary to have at hand not only a sufficient number of leukocytes, but also leukocytes of the proper quality. In addition, it is essential that it be in possession of opsonins, because without these bodies a reaction between the protecting cells and the invading bacteria cannot always be brought about. Conversely, it is true that a large content in opsonins cannot

FIG. 111.—LEUKOCYTE DEVOURING BACTERIUM.
O, indicates part played by opsonin.

¹ British Med. Jour., lxxiii, 1902.

² Proc. Royal Soc., London, lxxii, 1904. A brief discussion of opsonins has been given by Hektoen, in Science, February 12, 1909.

serve as an adequate protection if the leukocytes are inferior in number or power. The best results can only be obtained if these two factors are properly balanced. The opsonin content may be determined experimentally, the result being the so-called opsonin-index of the body. By treating an animal in a specific way, the number of its leukocytes and opsonin-content may be increased so that its power of resistance becomes much greater than ever before.

Diapedesis.—This term was originally applied to the passage of the blood or of its formed elements, chiefly the red cells, through the wall of a blood-vessel. Cohnheim, however, has shown in 1869 that this power of migration into the neighboring tissues is a distinct characteristic of the leukocytes. In contradistinction to the passive

FIG. 112.—DIAPEDESIS OF LEUKOCYTES.

behavior of the red corpuscles, the latter are aided in their escape from the vascular system by their ameboid properties. A delicate pseudopodium is first protruded through a perforation in the vessel wall, after which the principal mass of the cell is slowly drawn through the opening until entirely outside the vascular channel. An assemblage of great numbers of these corpuscles outside the main circulatory system results whenever a tissue has been injured or has become the seat of an infective process.¹ Under these circumstances, their migration is greatly facilitated by certain changes in the flow of the blood, namely:

(a) A relaxation of the capillaries in the area affected so that the size of the blood-bed becomes larger; (b) an accumulation of a larger quantity of blood in this particular region which tends to produce a local rise in temperature; and (c) a diminution in the velocity of the blood flow which enables the white corpuscles to assemble in numbers and to attach themselves more securely to the

vessel wall. These dynamical changes indicating an inflammatory reaction, may be studied under the microscope in such tissues as the mesentery, tongue, lung or web of the frog, if they are first moistened with normal saline to which a few drops of alcohol or a small amount of mustard has been added.

Having invaded the tissue, the leukocytes immediately display their phagocytic properties. Supposing that the inflammatory reaction has been produced by bacteria, the outcome of this interaction depends upon the relative strengths of the leukocytes and invading cell. If the latter is the more powerful factor, the infection will gradually extend to neighboring areas of the tissue, while if the former is the stronger, the bacteria will eventually be encircled and eliminated. But, in either case, large numbers of leukocytes will be destroyed in the course of this process, their remnants appearing in the extravasation in the form of pus-corpuscles. The foregoing discussion

¹Adami, *Inflammation*, Macmillan, New York, 1909.

clearly shows that the leukocytes constitute a most important safeguard against bacterial invasion. They are therefore directly concerned with the production of immunity.

In this connection mention should also be made of the fact that the mammalian body contains other types of phagocytes to which different names have been given. Contrary to the white corpuscles, which are migratory phagocytic entities, the cells now referred to remain "stationary." They are found, for example, in bony tissue where they have to do with the absorption and removal of all superfluous material, or in the spleen and liver where they take up the worn out red corpuscles and destroy them. To the first type of cells belong the myeloplaxes of the bone-marrow, while the second group is represented by the so-called giant cells and the third, by the endothelial lining cells of the hepatic capillaries, generally known as the "Sternzellen" of Kupfer. Since the aforesaid cells are so closely related in function, it is quite probable that they are also allied to the leukocytes in structure as well as embryologically.

Allied Functions.—Certain other functions have been ascribed to the white corpuscles, the most important of which is their power of taking up nutritive material and of carrying it to different parts of the body. Thus, the lymphocytes are said to absorb fat globules and to convey them into the lymph channels. They are also supposed to aid in the absorption of the peptones and to help in maintaining a proper protein content of the blood. Both functions are in keeping with their phagocytic properties. Sufficient evidence is also at hand to show that the leukocytes contain a substance which, when liberated, plays an important part in the coagulation of the blood.

CHAPTER XVIII

THE BLOOD PLATELETS

Physical Characteristics.—While the blood platelets are usually described as rounded biconvex discs, it must be granted that their shape varies considerably from almost globular to flat. They have also been observed to assume a spindle shape; in fact, it is stated that they possess this form normally in the horse. They give no particular color impression. Their granular centers refract very strongly, and stain deeply with basic dyes. For this reason, they are said to contain a real nucleus, and may therefore be regarded as true cells. They display ameboid movements, and if collected in a favorable medium, present a number of variegated processes. Their specific gravity is less than that of the other formed elements of the blood, which fact accounts for their occupying the outermost layers of the blood stream. As their diameter measures as a rule no more than 3μ , they

are scarcely half as large as the red corpuscles, but cells considerably larger or smaller than these are not uncommon. Their number is usually given as 180,000 to 800,000 per cu. mm., which means that they are more numerous than the leukocytes.

Methods of Examination.—A few platelets can always be secured by carefully collecting a drop of blood in normal saline solution; much better results, however, are obtained with Haymen's fluid.¹ Bizzozero² recommends a solution of 30 per cent. gentian violet in a 0.75 per cent. sodium chlorid solution. Their immediate fixation may be achieved by drawing the blood into a 1 per cent. solution of osmic acid, or better still, by previously moistening the tip of the finger from which the blood is to be taken with this solution.³ Deetjen preserves them by permitting a droplet of blood to flow upon agar jelly.⁴ By making use of their slight specific gravity, Bürker⁵ separates them from the other formed elements in the following manner. A drop of blood is collected upon a thin sheet of paraffin and is allowed to stand for a short time. The lighter platelets collect near the surface of the drop and may be removed by drawing a cover-glass through its upper layers.

FIG. 113.—THROMBOCYTES
HIGHLY MAGNIFIED.

Origin and Fate of the Blood Platelets.—Haymen, their discoverer, regarded the thrombocytes as carriers of hemoglobin and therefore as transitional types of the red corpuscles. He designated them as hematoblasts. Bizzozero, on the other hand, first expressed the view that they are independent elements and

are therefore neither embryonic red cells nor the remnants of destroyed corpuscles. To be sure, fragmented red cells may appear in the blood at times, but a differentiation between these bodies and the blood platelets, as described by Bizzozero, is readily possible upon the basis of their histological characteristics. The supposition that the thrombocytes are fragmentary white corpuscles also lacks satisfactory confirmation. Thus, it is a well-known fact that the latter do not disintegrate in great numbers in the circulating blood and neither do they break up with undue rapidity in shed blood. It may indeed be concluded that they are relatively resistant, because they are often preserved in extravascular and intravascular coagula of long standing.

The conclusion, that the thrombocytes are not derived from the

¹ Archives de physiol. norm. et pathol., x, 1878.

² Virchow's Arch. für path. Anat., xc, 1882.

³ Kemp, Stud., Biol. Lab., J. Hopkins Univ., iii, 1886.

⁴ Made by dissolving 5 gr. of agar-agar in 500 c.c. of distilled water. To 100 c.c. of the filtrate are added 0.6 gr. NaCl solution, 6 to 8 c.c. of a 10 per cent. NaPO₃ solution and 5 c.c. of a 10 per cent. K₂HPO₄ solution. See: Deetjen, Virchow's Archiv, clxiv, 1901, 260.

⁵ Pflüger's Archiv, cii, 1904, 36.

other formed elements of the blood, makes it necessary to examine the evidence pertaining to their origin somewhat more closely. It is believed (a) that they are not present in the normal circulating blood, and appear only if the latter is brought in contact with a foreign body, and (b) that they are preëxisting and constant constituents of the blood. The former view contends that the thrombocytes do not belong to the class of the formed elements, but appear together with those chemicophysical alterations which indicate the beginning of the coagulation of the blood. They constitute, so to speak, condensation or precipitation products of the globulin constituents of the blood. This view¹ has found support in the following observations. It is true that the platelets are absent from the blood of several animals, for example, from that of the frog, fishes and birds. It is also conceded that they are not very conspicuous in the blood of several mammals, but may be rendered more prominent in these animals by first injuring the wall of one of their blood-vessels or by introducing a foreign body into their circulatory system. Under these conditions they may be seen to collect upon the injured area in the form of a deposit. Moreover, Buckmaster has shown that blood drawn into the sterile serum of another animal, does not always display these bodies, but exhibits them very promptly if it is collected in the loop of a platinum wire. Furthermore, while they are not present in fresh plasma which has been rendered non-coagulable by sodium oxalate or peptone, they appear in this plasma in large numbers after it has been cooled for a period of about 24 hours. Lastly, blood which has been treated with an anticoagulating agent while still in the circulatory system, does not show them, nor do they appear in it later on after its withdrawal from the body.

The evidence which may be submitted in favor of the second view, advocating the preëxistence and independency of the thrombocytes, is as follows: Quite aside from the fact that we are in possession of definite methods for their isolation, we possess in the mesentery of the guinea-pig and in the wings of the bat preparations in which it is possible to observe them directly. Moreover, they are present in large numbers in the blood-vessels of the subcutaneous connective tissue of various animals and particularly in that of the new-born rat. If to these facts are added the observations regarding their ameboid motion,² as well as certain observations pertaining to their physical and chemical characteristics, such as their stickiness, their great vulnerability and their very manifest power to incite the coagulation of the blood,³ it cannot be doubted that they are preformed and functionally distinct constituents of the blood.

¹ Wooldridge, *Die Gerinnung des Blutes*, Veit and Co., Leipzig, 1894, and Loswit, *Virchow's Archiv für path. Anat.*, cxvii, 1889.

² Deetjen: *Virchow's Archiv für path. Anat.*, cxlvi, 1901, and Deckhuysen, *Anatom. Anzeiger*, xix, 1901.

³ Eberth and Schimmelbusch, *Die Thrombose*, Stuttgart, 1888, and Klopsch, *Anat. Anzeiger*, xix, 1901.

The red and white corpuscles having been excluded as possible sources of the thrombocytes, their origin remains much in the dark. Wright, however, has suggested that they arise from the cytoplasm of the giant cells, the so-called megakaryocytes, which are found in the marrow of the bones. It is believed that these cells send out pseudopodia which become detached and are carried away in the bloodstream. The observations of Duke¹ and others tend to show that the life of the thrombocytes is very short.

When the blood is shed, the platelets quickly agglutinate, forming globular or irregular masses. Their formerly pointed processes become stubby and break off, while their central portions swell up and rupture. Eventually, therefore, the platelets are reduced to chips of insignificant size, many of which soon disappear altogether by dissolution, but the regions in which the thrombocytes have undergone this disintegration, soon become the seats of active fibrin-proliferation. In this way definite centers of coagulation are formed, from which the different shreds of fibrin gradually extend through the blood in all directions. Practically all the platelets take part in this process so that they finally become intricate constituents of the network of fibrin. The red and white corpuscles, on the other hand, remain normal, because the shreds of fibrin pass by them without actually imbibing them. It has been proven by Bürker² that the number of the thrombocytes is proportional to the mass of the fibrin formed, and that this reaction may be varied by changes in temperature as well as by the addition of chemicals. Thus, any agent tending to cause a destruction of the thrombocytes, also hastens the coagulation of the blood, while any substance possessing preservative qualities, not only retards this process, but actually prevents it. The latter end may be attained very readily by the addition of hirudin,³ because this substance preserves the thrombocytes. It must be conceded, therefore, that, quite irrespective of the red and white corpuscles, the disintegration of the platelets gives rise to an agent which plays a most important part in the coagulation of the blood. This activating substance is designated as thrombokinase.

¹ Jour. of the Amer. Med. Assoc., lv, 1910.

² Pflüger's Archiv, cii, 1904, 36.

³ A crystallized form of the extract of leeches. The heads of these animals contain the active principle, an albuminous body.

CHAPTER XIX

THE COAGULATION OF THE BLOOD

A. EXTRAVASCULAR CLOTTING

Physical Changes in Coagulating Blood.—Possibly the most striking characteristic of the mammalian blood is its power of changing its fluid state into one of semisolidity. As this conversion, designated as coagulation, may set in either after the blood has escaped from the blood-vessels, or while still within them, two forms of clotting are obtained, namely, the extravascular and the intravascular.

FIG. 114.—THE COAGULATION OF THE BLOOD.

A, Normal blood; B, the formation of fibrin from colonies of thrombocytes enveloping the formed elements; C, the separation into the coagulum and supernatant serum.

In normal blood the different corpuscular elements are freely suspended in the plasma. When coagulation sets in, delicate shreds of fibrin are formed which advance from certain fixed points and traverse the blood in different directions, encircling large colonies of corpuscles. In accordance with the view of Wooldridge, these filaments arise in consequence of a deposition of fine crystals which become confluent and are finally united into an extensive network. The production of fibrin, therefore, is essentially a process of crystallization, so that the coagulation of the blood may be said to be based upon the crystallization of fibrin from a supersaturated solution. The physical characteristics of these crystals, as well as their functional properties, make it certain that they are retained in a liquid state and should therefore not be considered as solids. The meshes of this network are gradually drawn more closely together so that the corpuscular elements become more tightly packed. The entire mass finally gravitates to the bottom of the receptacle. This gelatinous deposit is known as the coagulum. It is composed of fibrin, the different types of corpuscles, and nutritive material.

If the blood is permitted to clot slowly, so that a complete deposition of the red cells is had, the coagulum presents a marginal zone,

the color of which varies between yellowish gray and reddish gray. It is composed in the main of fibrin and colorless corpuscles and seems to originate in any blood in consequence of certain peculiarities in its manner of coagulating. The name of "buffy coat" or *crusta inflammatoria*, has been applied to this region.

The liquid which separates from the clot in constantly increasing quantity, is known as the serum. While its immediate source is the plasma, it differs from it materially, because it contains no corpuscular nor larger nutritive elements. The separation of the blood into the clot and the serum begins as soon as coagulation sets in, but is not completed as a rule until about 24 hours later. During this time the

FIGS. 115 AND 116.—THE FIBRIN NEEDLES FORMED IN THE CLOTING OF BLOOD. PLASMA OF OXALATED DOG'S BLOOD CLOTTED BY THROMBIN. THE PHOTOGRAPHS SHOW THE NEEDLES AS SEEN WITH THE ULTRAMICROSCOPE.

A, photographed by sun-light; B, by arc-light. Only the needles lying in the focal plane are seen distinctly. (Howell.)

fibrin shreds contract more and more and squeeze additional amounts of serum out of the clot. If the vessel into which the blood is withdrawn is kept in a cool place and is not disturbed, the serum separates as a clear, straw-colored fluid. It frequently happens, however, that the clot adheres to the walls of the receptacle and is torn, releasing varying numbers of red and white corpuscles. The serum then assumes a reddish color and acquires a specific gravity which is much greater than that of clear serum.

Chemical Changes in Coagulating Blood.—While the final and most important change effected during coagulation is the formation of fibrin, this body cannot be obtained unless several preliminary reactions have first been completed. Indeed, the process of clotting may be divided

into two stages, the first ending with the formation of thrombin and the second with the production of fibrin. Fibrin as such is not present in the circulating blood, but is derived from a precursor through the intervention of thrombin. The substance from which fibrin arises, is known as fibrinogen and is present as such in the plasmatic portion of normal blood. Fibrinogen, however, is an inert body and must first be activated before its conversion into the final product, fibrin, can be achieved. This activation is made possible solely with the help of a fibrin "ferment," commonly designated as thrombin.

Thrombin as such is not present in normal blood, but is formed from an inactive precursor, called thrombogen or prothrombin. The conversion of the latter into its active form is accomplished by means of an organic thromboplastic agent, called thrombokinese, in the presence of soluble calcium. The kinase is furnished by the cellular elements of the blood, principally the thrombocytes. To recapitulate, the circulating blood contains fibrinogen, thrombogen and soluble calcium salts. If the blood is brought in contact with a foreign body so that a destruction of the thrombocytes results, thrombokinese is liberated which, with the help of ionic calcium, activates the thrombogen into thrombin. This process constitutes the first phase of coagulation. Its completion in turn insures the second phase which consists in the conversion of fibrinogen into fibrin.

This explanation of the process of clotting is in accordance with the views expressed by Moravitz,¹ Fuld and Spiro,² and is based upon data which have been furnished in large part by Schmidt, Wooldridge, Pekelharing, and Hammarsten. While this view is open to several objections, especially in regard to the action of thrombin, it is the one commonly accepted to-day. A second explanation, which is in part

¹ Hofmeister's Beiträge, iv, 1903, 381; also see: A. Schmidt, Zur Blutlehre, Leipzig, 1892 and Wiesbaden, 1895.

² Ibid., v, 1904, 171.

dependent upon the work of Wooldridge and others, has recently been advocated by Nolf¹ and Howell.² It is held that prothrombin may be changed into thrombin by means of calcium alone, but this reaction is prevented ordinarily by an antithrombin³ which is always present in the blood. If the blood is injured, a thromboplastic substance is liberated by the corpuscles (platelets), which neutralizes the action of the antithrombin and allows the activation of the prothrombin by the calcium. The second stage of coagulation takes place as described previously. The theories just outlined, therefore, differ only in regard to the action of the "kinase" which, on the one hand, is said to act as a ferment which actually takes part in the activation of the prothrombin, and, on the other, is believed to inhibit the anticoagulating substance so that the calcium is able to incite the reaction.

Thrombokinase.—As it has not been possible so far to demonstrate an organic kinase in the plasma of the blood, it is commonly held that this clotting agent is contained in the formed elements. For this reason, a disintegration of the latter must necessarily precede the liberation of this substance, but as relatively few red cells are destroyed during the shedding of the blood, it may be concluded that these elements cannot possibly harbor the coagulating agent. It has also been observed that these cells are quite ineffective under ordinary conditions, but may be changed into a coagulating agent if the hemoglobin is thoroughly separated from the stroma. With the help of the latter even intravascular clotting can readily be effected. Practically the same statement may be made regarding the white corpuscles. It is true, however, that under experimental conditions clotting may be greatly accelerated by the addition of leukocytic material. But this fact cannot be employed as a strong argument in favor of the view that they do play a part in normal clotting, because they are found in large numbers in exudates in which coagulation has not taken place. And furthermore, plasma from which the leukocytes and red cells have been removed by centrifugalization, may be made to clot by the addition of water or by passing a current of carbon dioxide through it. Wooldridge, moreover, has shown that the white cells of lymph, when washed in salt solution, are quite unable to clot the lymph from which they have been taken and neither can they coagulate peptone-plasma in the absence of platelets or their derivatives.

The thrombocytes, on the contrary, have been shown to exert a most important influence upon coagulation, because they disintegrate very rapidly in shed blood and the amount of fibrin formed is nearly proportional to the number of platelets destroyed. Various experiments may be cited in support of this statement. Thus, it is possible to increase or to decrease their destruction by subjecting them to different temperatures or to different mechanical and chemical influences. In general, it holds true that a medium which tends to preserve them, delays the coagulation, while a medium which is injurious to them, hastens this process. For example, if a drop of a solution of ammonium oxalate (1/100 N) is added to a drop of blood, coagulation fails to take place. If this sample of blood is examined later on, it will be found to contain the thrombocytes in a state of perfect preservation, while the red and white corpuscles are thoroughly fragmented. Moreover, Schmidt has called attention to the fact that the plasma derived from sedimented horse-blood, exhibits a difference in its coagulability in so far as its upper portion clots more readily than its lower, but may be made to remain fluid for a much longer time than the latter by passing it through a filter. In explanation of this

¹ Archives intern. de physiol., ix, 1910, 407.

² Am. Jour. of Physiol., xxix, 1911, 29.

³ Called hepatothrombin by Nolf.

phenomenon, it may be stated that the thrombocytes, on account of their lesser specific gravity, collect in much greater numbers near the surface of the plasma and that they may then be removed from it by filtration. Bizzozero beat freshly drawn blood with cotton threads until they were thoroughly covered with platelets. They were then washed in a 0.7 per cent. solution of sodium chlorid to remove the red corpuscles. If desired, a rapid coagulation of artificial prothrombin could then be effected by suspending these threads in solutions of this substance. To prove his point more conclusively, he showed subsequently that this result cannot be obtained with the cotton threads alone, while threads covered with red cells or with leukocytes, gave rise, at best, to only a very slow type of coagulation. Moreover, it has been observed repeatedly that the disintegrating thrombocytes act as centers for the formation of fibrin, and that the injection of platelets into the circulation produces intravascular clotting. It must be concluded, therefore, that the platelets yield a substance which serves as the exciting agent of the coagulation.

Morawitz calls this agent thrombokinase, but it is also referred to as cytocym. If it is assumed that the platelets are not real cells but merely fluid crystals, the liberation of the thrombokinase would correspond to the deposition of these crystals as insoluble threads of fibrin. For the present, however, it seems best to adhere to the view of Morawitz, Fuld and Spiro as previously outlined. In accordance with this explanation, it becomes necessary to assume further that the blood of those animals which does not clot when collected directly from the blood-vessel, contains no thrombokinase. The absence of this agent is readily accounted for, because these animals are not in possession of thrombocytes. Instead, their tissues contain a very effective thromboplastic substance which takes the place of thrombokinase and which is brought in contact with the blood as it flows across the opened surface. But, the mere fact that in us and allied animals the principal coagulating agent is held in the blood itself, does not preclude the possibility of a similar substance being present in our tissues; in fact, it seems entirely probable that we are thus doubly protected.

Thrombogen is a normal constituent of the plasma. Only a part of it is used up during coagulation. The remaining portion escapes activation either because a sufficient quantity of thromboplastic material to cause its complete conversion is not at hand, or because its formation is stopped as soon as the coagulation has advanced to a certain stage. It is not present in the tissues, and the indications are that it is not derived from the cellular elements of the blood, but is held in solution in the plasma. Drinker¹ believes that it arises in the bone-marrow, because it may be removed from the latter in considerable amounts by perfusion. It is very stable and is capable of withstanding the temperature of boiling water for a brief period of time. Although calcium is necessary to incite its conversion into thrombin, this salt is by no means the precursor of thrombin. Thrombogen is also known as prothrombin, proferment or plasmozym.

Thrombin, or fibrin ferment is not a preëxisting constituent of the blood nor of any one of the fluids of the body. Thus, if blood is withdrawn directly into an excess of alcohol, the precipitate, when dried, pulverized, and extracted with water, yields practically no thrombin. While it is usually regarded (Schmidt) as an enzyme or ferment, it must be remembered that an agent of this kind possesses the property of producing maximal reactions even when present in minute amounts. Another peculiarity of enzymes is their power of producing a chemical reaction without losing any of their substance. Butas Wooldridge, Nolf and Rettger² have failed to observe these peculiarities in thrombin, its ferment nature has not been definitely established. Indeed, the evidence seems to point rather the other way, because it has been found that the amount of thrombin is directly proportional to the amount of fibrin formed, as the following compilation will show:

¹ Am. Jour. of Physiol., xli, 1916, 5.

² Am. Jour. of Physiology, xxiv, 1909, 429.

5 drops of thrombin yield 0.2046 gm. of fibrin.
10 drops of thrombin yield 0.3575 gm. of fibrin.
20 drops of thrombin yield 0.6089 gm. of fibrin.
40 drops of thrombin yield 1.5872 gm. of fibrin.

Besides, it has been noted that thrombin actually becomes a part of the final product, and that this reaction does not vary with the temperature, *i.e.*, it takes place at 17° C. as well as at 40° C. Rettger, therefore, draws the conclusion that fibrin is not derived exclusively by a progressive conversion of the fibrinogen, but may also be produced by a direct combination of these bodies. The product, however, is unstable, because the thrombin may be separated from it with relative ease. Thrombin may also be prepared in accordance with the directions given by Schmidt.¹ A certain quantity of blood having been permitted to clot, the serum is precipitated by the addition of 15 to 20 volumes of alcohol, in excess. The precipitate is removed after several days or months and is dried, pulverized and extracted with water. While this solution contains different protein bodies and salts, it may be concluded that the coagulation which it induces when added to solutions of pure fibrinogen, is caused by its thrombin constituent. Buchanan and Gamgee advise to extract the ordinary washed fibrin for several days with an 8 per cent. solution of sodium chlorid. The filtrate is not pure, but contains dissolved proteins in addition to much thrombin. Howell² purifies this extract by shaking it repeatedly with chloroform. In this way, the coagulable proteins are removed, while the thrombin is left behind in a pure state, although somewhat diminished in quantity. This author states that it is easily soluble in water and is not coagulated by boiling. Moreover, while it is difficult to precipitate it with alcohol in excess, it may be precipitated with ammonium sulphate in half saturation. As it gives positive results with several of the ordinary protein reagents, it must be regarded as a protein substance.

Fibrinogen exists as an independent body in the plasma of the circulating blood. It is also present in lymph, chyle, and certain transudates and exudates, but not in the blood serum, inasmuch as it is used up in the process of clotting. While its place of origin is not definitely known, it is certain that it is not derived from the corpuscular elements of the blood. It should be mentioned, however, that some evidence is at hand to show that it may be formed in the liver and in the myeloid tissue of the bone-marrow. Thus, Nolf has found that the quantity of fibrinogen in the blood may be greatly diminished by extirpating the former organ or by the administration of poisonous amounts of phosphorus or chloroform. Mention should also be made of the observation of Dastre that the blood of the mesenteric vein is richer in fibrinogen than that of the corresponding artery. This fact has been interpreted as showing that the intestinal wall is one of the sources of this substance.

Fibrinogen may be obtained in solution and free from other proteins in the following manner: A quantity of fresh blood is mixed with a solution of sodium oxalate in amounts sufficient to give a 0.1 per cent. oxalate mixture. The latter is then centrifugalized and its plasma portion precipitated by the addition of an equal amount of a saturated solution of sodium chlorid. The resulting precipitate of fibrinogen is pressed out or centrifugalized, redissolved in an 8 per cent. salt solution, and the filtrate precipitated by a saturated salt solution. Having been subjected to this process three times, the final precipitate is pressed between filter paper and is then finely divided in water. The precipitate may be dissolved in a 1 per cent. solution of sodium chlorid. If it does not dissolve readily, a few drops of a 0.5 per cent. solution of sodium bicarbonate should be added. The traces of sodium oxalate may be removed by dialysis in a collodion sac, against a 1 per cent. solution of sodium chlorid.

¹ Pfüger's Archiv, xi, 1887, 515.

² Am. Jour. of Physiol., xxvi, 1910, 26.

A pure solution of fibrinogen may be kept at ordinary temperatures for an indefinite period of time without its yielding even traces of fibrin. A perfectly typical coagulum, however, may be produced, if either a washed fibrin-clot, a small quantity of blood serum, or a solution containing thrombin is added to it.

Fibrinogen is a protein. It belongs to the group of the globulins. From paraglobulin, it may be distinguished in several ways; viz.: it coagulates at a lower temperature (55° to 60°), is completely precipitated by saturation with sodium chlorid or magnesium sulphate, and may be converted into the insoluble protein, fibrin. Its percentage composition has been given by Hammarsten as: C 52.93, H 6.90, N 16.66, S 1.25, O 22.26. According to Schmiedeberg its molecular composition is: $C_{108}H_{162}N_{30}SO_{34}$.

Fibrin.—In accordance with the analyses of Hammarsten, fibrin possesses the same composition as fibrinogen. This similarity, however, is only an apparent one, because as both substances are extracted with alcohol and ether, the fat and lipid are not included in the analysis, and hence, the remaining substance appears as a protein of the composition just given. Wooldridge,¹ in fact, believes that these bodies are not identical at all but show certain differences in the lipid part of their molecules. Fibrinogen as it exists in the plasma is regarded as a lecithoprotein or as a substance containing much phospholipin. Fibrin is similarly constituted, but contains less phospholipin. The chemical process underlying the formation of the relatively insoluble fibrin is not clearly understood. Fibrinogen is said to change first into soluble fibrin, and later on into fibrin proper. In accordance with Hammarsten,² a hydrolysis results which splits the molecule of the fibrinogen into fibrin and fibrinoglobulin. Other investigators, however, assume that physicochemical alterations are incited which lead to an intramolecular rearrangement of the fibrinogen. Thus, fibrinogen is regarded as the hydrosol, and fibrin as the hydrogel of one and the same globulin.³ It is also supposed that a precipitation of the fibrinogen by electrolytes takes place soon after the thrombin has incited its decomposition.⁴

If the blood is beaten with a rough piece of wood while it is being withdrawn from the blood-vessel, the fibrin accumulates upon the stick in the form of an elastic fibrous mass, the springiness of which is lessened as soon as the shreds are torn or are separated from their attachments. This deposit is always contaminated with red corpuscles and lymphoid cells. If it is essential to obtain this substance in a pure form, it should be prepared from filtered plasma, or from filtered transudates; moreover, it should be noted that if it is allowed to remain in contact with the blood from which it has been removed, it dissolves in part. While the factors which are responsible for this fibrinolysis are not known, it is believed that they are of enzymic origin. Fibrin derived from the blood of different animals, exhibits somewhat different properties. It is insoluble in water, alcohol and ether, but may be dissolved in dilute salt solutions at a temperature of 40° C.

B. INTRAVASCULAR CLOTTING

It has been found that the blood retains its fluid condition only as long as it is permitted to remain in contact with the normal intima of the blood-vessels. This statement implies that coagulation must set in as soon as the blood is brought in relation with a foreign body, whether this be outside or inside the vascular channels. Intravascular

¹ Collected papers, Rep. to the Scient. Comm. of the Grocer's Assoc., i, 201; ii, 266.

² This view is also held by Schmiedeberg (Archiv für Exp. Path. und Pharm., xxxix) and Heubner (ibid., xlix, 1903, 229).

³ Iscovesco, Soc. Biol., lx and lxi, 1906.

⁴ Friedemann and Friedenthal, Zeitschr. für exp. Path., iii, 1906, 73.

clotting may be incited by introducing a solid object directly into the blood-stream, or by causing a trauma of the blood-vessel and surrounding tissue so that these will be changed into destructive agents. A thin layer of fibrin is then deposited upon the injured area, more and more material being gathered in gradually until a clot has been formed which may occlude the entire lumen of the blood-vessel. When fully formed, a clot of this kind is known as a thrombus. After the blood current has played against this intravascular coagulum for some time, pieces of it may be broken off and carried to distant parts of the circulatory system, where they may obstruct the blood flow and give rise to an anemia and functional uselessness of the tissues situated distally to the block. A floating thrombus is known as an embolus.¹ The ultimate outcome of a condition of this kind depends upon the freedom with which the tissues so cut off may be supplied with blood by anastomosing vessels. It need scarcely be mentioned that the lining of the blood-vessels may also be changed into a destructive agent by the products of bacteria, and other toxic substances circulating through the system.

Intravascular clotting may also be incited experimentally by the injection of solutions of various substances. In accordance with the statements made previously, it might be supposed that thrombin or thromboplastic substance would act as very powerful coagulating agents when introduced into the circulation, but, curiously enough, the system possesses the power of protecting itself against them. Howell believes that the action of thrombin is neutralized in this case by a greater production of antithrombin.

The effects obtained with tissue extracts and solutions of thromboplastic substance are rather perplexing. Extensive clotting most frequently results in consequence of the injection of moderate amounts of thrombokinase and extracts of organs rich in cellular elements, such as the thymus and lymph glands. It has been suggested by Woolbridge that these extracts contain thrombokinase. Their injection, therefore, leads to the same results as the liberation of this body in shed blood. It is to be noted, however, that small quantities of these extracts diminish the coagulability of the blood. The former reaction is usually designated as the positive and the latter as the negative phase of the injection, but as a lessening of the coagulability cannot be obtained in this manner during extravascular clotting, it must find its origin in certain functional peculiarities of the tissue cells, analogous to their behavior toward toxins. It is a well-known fact that the injection of diphtheria toxin gives rise to a certain amount of antitoxin in the course of two or three days. Additional injections, however, most generally produce a complete disappearance of the antitoxin until, a day or two later, it again makes its appearance in quantities much larger than those present before the second injection. It should

¹ The circulation may also be obstructed by embolisms of different origin, for example, by droplets of fat or bubbles of air.

also be mentioned that the effects of Witte's peptone, or of hirudin are only temporary. It seems, therefore, that certain tissue cells possess the power of rendering these substances inert, the probability being that this neutralization is brought about by the discharge of an anti-coagulating agent.

The fact that the blood does not clot while traversing the normal circulatory channels, may therefore be explained in two ways, namely: (a) by saying that thrombokinase is not liberated as long as the blood is prevented from coming in contact with a destructive agent and (b), that a certain amount of an anticoagulating substance is always present in the blood which serves the purpose of retaining the thrombin in its inactive condition.

THE TIME OF COAGULATION

The period intervening between the moment of the withdrawal of the blood and the moment when it has assumed a jelly-like consistency, is known as the coagulation time. Various methods have been devised to determine its length, but none of them gives absolutely reliable results. Vierordt¹ employed a glass tube possessing a diameter of 1 mm. and a length of 5 cm. A white horse hair having been placed lengthwise in this tube, the latter was then filled with the blood to be tested. After a few moments the hair was withdrawn at intervals and a short distance each time, until small coagula began to adhere to it. Possibly the simplest procedure is to collect a small quantity of blood in a test tube of ordinary size, noting the time of its withdrawal, and to determine again the moment when it is possible to invert this tube without causing the blood to flow out. Brodie and Russell² advocate the following method: A drop of freshly drawn blood is placed upon the polished tip of a conical piece of glass (Fig. 117). The latter is then inverted and placed in a small compartment underneath a lens magnifying thirty diameters. Very weak currents of air are brought to bear upon the lateral surface of this suspended drop at intervals of thirty seconds until the corpuscles cease to spin around and the external layers have assumed a gelatinous consistency. Bürker³ employs a glass slide the central area of which is depressed and surrounded by a low wall of glass. A drop of boiled water is then placed in this compartment, to which is added a drop of fresh blood. The time of mixing these fluids is accurately recorded by means of a kymograph and

FIG. 117 —COAGULATION TIME OF BLOOD.

A, chamber in which drop is suspended from surface of cone (B) under ocular of microscope.

¹ Archiv für Heilkunde, 1878, 193.

² Jour. of Physiol., xxi, 1897, 403; also see: Pratt, Archiv für Exp. Path. und Pharm., xlix, 1903, 299.

³ Pflüger's Archiv, cii, 1904, 57.

Jaquet chronometer. At intervals of half a minute the hair-like end of a glass rod is drawn through this mixture from side to side until it catches the first shreds of fibrin. This moment is again noted. Cannon and Mendenhall¹ have devised a small instrument, known as a graphic coagulometer, consisting of a horizontal writing lever and a vertical glass tube containing the blood to be tested (Fig. 118). A coil of very thin copper wire is suspended in this blood, its other end being attached to the tip of the lever. The latter is counterpoised in such a manner that it retains its horizontal position without supports as soon as the blood is coagulated. This procedure, therefore, consists in releasing the lever at intervals of 30 seconds until its pointer fails to rise.

The experiments of Vierordt have shown at an early date that the coagulation time of human blood is subject to considerable daily variations. During the morning hours, he found its value to be 9.6 minutes,

FIG. 118.—GRAPHIC COAGULOMETER.

A, writing lever counterpoised by weight W and supported at S and R; P, rod by means of which supports may be removed; C, wire which rests with its ring-like end; D, in blood drawn into cannula C.

after the noon-day meal 10.1 minutes, and in the evening 8.1 minutes. This investigator, however, did not protect the blood against changes in the temperature of the air and also failed to detect the first indications of clotting with any degree of accuracy. For this reason, his tests have led to values which are somewhat higher than those submitted by other investigators. Bürker, who repeated these experiments under more favorable circumstances, obtained values ranging between 6 and 12 minutes. The latter were gotten in the morning and the former in the evening.

The coagulation time differs considerably in different individuals. Hewson states that the average time is 3 to 4 minutes, while Gendrin gives it as 10 minutes. Bürker, however, found a rather close agreement, but only after he had thoroughly controlled such factors as age, sex, temperature and the time of day. His values range between 6 and 7.5 minutes. Those of Cannon and Mendenhall average 4.9 minutes. The first signs of clotting usually appear within 3 or 4 minutes after the withdrawal of the blood. The average time in the dog and cat is 2.5 to 4 minutes.

¹ Am. Jour. of Physiol., xxxiv, 1914, 225.

Some persons, who are known as bleeders, exhibit a decided tendency toward delayed clotting which frequently endangers their life (hemophilia). Hemorrhages from the mucous surfaces may occur almost at any time and without apparent cause. Extravasations may also result into the subcutaneous tissue and the joints, as well as into the different serous cavities of the body. This condition, the cause of which is unknown, is inherited and usually destroys the male line, *i.e.*, it remains dormant in the females but may be transferred by them to their male offsprings.

CONDITIONS INFLUENCING THE COAGULATION TIME

Temperature.—In general it may be said that high temperatures accelerate and low temperatures retard the clotting. For this reason, hot cloths are often applied to bleeding surfaces, the heat acting merely as an agent to intensify the chemical changes underlying the process of coagulation. Conversely, a sample of blood may be retained in its fluid condition for a relatively long period of time by surrounding the receptacle in which it is kept with crushed ice. This result may be made the more striking if blood is used, the normal clotting time of which is long; for example, that of the horse or that of invertebrates. If blood is heated to 60° C., it loses its power of coagulation, because the fibrinogen is precipitated at this temperature.

The effect of heat and cold seems to be directly proportional to the destruction of the thrombocytes, but while these elements disintegrate more readily at high than at low temperatures, they are also broken up at the temperature of the body. The fact that the blood of cold-blooded animals clots very slowly is frequently cited as proving that low temperatures tend to retard the coagulation, but it is more than likely that this is merely a coincidence and that the correct explanation is to be sought in fundamental differences in the manner of clotting of this type of blood.¹

Methods of Collecting the Blood.—If the blood is drawn into a receptacle with a smooth surface, it does not clot so readily as if collected in one possessing a rough surface. It is also true that the coagulation sets in more quickly in a receptacle which presents a large area to the blood. For this reason, the clotting may be greatly retarded by oiling the walls of the vessel or by coating them with wax, paraffin, or agar. In explanation of these differences it need only be mentioned that the liberation of the activating agent depends primarily upon the destruction of the thrombocytes. Quite naturally, an oiled receptacle or one possessing a small surface, must be less injurious to these cells than one presenting the opposite characteristics.

The same explanation holds true in the case of blood which is retained in its fluid state by surrounding it with the normal lining of the blood-vessel. Thus, if a certain segment of a vein is filled by

¹ L. Loeb, *Archiv path. Anat.*, clxxxv, 1906, 160.

placing a ligature upon its central end and is then excised after having previously ligated its distal end, the blood so entrapped remains fluid for many days. This preparation, which is known as the "living test tube," must be kept under proper conditions of moisture and temperature, because if its walls are injured, it will act in the same manner as any other foreign body and cause intravascular clotting. If this preparation is suspended for a time, the red corpuscles finally settle by gravity, so that it is possible to obtain the supernatant liquid separately and to subject it later on to coagulating agents.

Air was formerly regarded as a necessary factor in coagulation, but as this process also takes place in blood which has been collected in a tube above mercury, this view can no longer be held. Accumulations of air in the form of larger or smaller bubbles act as foreign bodies and hasten the destruction of the thrombocytes and the liberation of thrombokinas.

Substances Derived from the Tissues.—The observation has been made repeatedly that the blood of certain animals, when prevented from coming in contact with the neighboring tissues, clots less speedily or remains fluid for sometime after its withdrawal. This is true especially of the blood of birds, reptiles and fishes, which clots rather quickly if permitted to flow across the incised tissues, but fails to coagulate for many days if drawn from the cannulized blood-vessel directly into a clean and dust-free beaker. This result indicates that the blood of these animals is devoid of a coagulating agent, although a substance of this character is contained in their tissues. The plasma obtained from this type of blood also remains fluid for a long time, but coagulates within a few minutes if an extract of the tissues is added to it. Under ordinary conditions, however, an animal of this kind is fully protected against serious hemorrhage, because the escaping blood is subjected to the coagulating agent as soon as it leaves the vascular channel.

Different extracts have been prepared from the tissues of mammals which markedly accelerate the coagulation of the blood. The active principle contained in them has been variously designated as cell-globulin, tissue-fibrinogen, tissue nucleoproteid, coagulin, and zymoplastic substance. Howell¹ suggests the term of thromboplastic substance, because it permits of a more general application, and refers merely to an agent which accelerates the clotting without indicating the manner in which this acceleration is brought about. A substance of this character has been obtained by Howell from certain tissues with the help of ether or with ether and alcohol. It is known as kephalin, and is held in combination with a protein which is precipitated at a temperature of 60° C. According to Howell, this body possesses the property of neutralizing the antithrombin, while others² believe that it is identical with fibrin ferment and that the activation of the pro-

¹ *Am. Jour. of Physiol.*, xxxi, 1912, 1.

² Moravitz, *Hofmeister's Beiträge*, v, 1904, 133.

thrombin to thrombin is facilitated by it. It is held, however, that fibrin ferment as such is not present in the tissues.

Admixture of Neutral Salts.—When present in small amounts, the neutral salts act rather favorably upon coagulation, but tend to retard this process as soon as their quantity surpasses a certain minimum. Thus, a 27 per cent. solution of magnesium sulphate prevents the clotting for a long time, if 1 part of it is added to 3 or 4 parts of blood. Sodium sulphate in half-saturated solution manifests a similar action, but it must be mixed with an equal quantity of blood. In all these instances the corpuscles settle very slowly, but their deposition may be hastened by centrifugalization. The supernatant plasma, known as "salted plasma,"¹ may be made to clot later on by diluting it sufficiently with water or by the addition of a few drops of a solution of thrombin. If the "salted" blood is left standing for a day before it is centrifugalized, the plasma does not clot.

Bürker emphasizes the fact that weak solutions of magnesium sulphate tend to preserve the thrombocytes, so that it is possible to obtain them from the supernatant plasma long after the red cells have separated out. The deduction, therefore, seems justified that weak solutions of the neutral salts inhibit the formation of the thrombin, while strong solutions prevent the interaction between this agent and the fibrinogen.²

Weak solutions of sodium chlorid do not influence the coagulation, while concentrated solutions of this salt manifest an action similar to that of the salts mentioned previously. Thus, it is possible to prevent the clotting by drawing the blood into an equal volume of a 10 per cent. solution of this salt. Sodium carbonate in concentrated solution and bile salts also retard this process.

Decalcification of the Blood.—Arthus and Pages³ have shown that the blood from which the calcium has been removed, remains fluid for an indefinite period of time. This end may be attained by collecting it in a 0.1 to 0.3 per cent. solution of sodium or ammonium oxalate. It should be remembered, however, that it may be made to clot at any time subsequently by adding a proper amount of a calcium salt to it. Furthermore, it has been shown that the mere presence of dissolved calcium is not sufficient to incite clotting, but that it must be made available in the form of a salt held in an ionized state, for example, as calcium chlorid or sulphate. The oxalated blood may be subjected to centrifugalization, after which the plasma derived from it, may be treated in the same manner as other non-coagulable plasmas. Thus, horse-blood containing 0.1 per cent. sodium oxalate, will yield a perfectly clear, yellowish plasma which displays no tendency to clot under ordinary conditions. But if this plasma is warmed and mixed with a solution of calcium chlorid drop by drop in excess, it will give

¹ A. Schmidt, *Zur Blutlehre*, Leipzig, 1892.

² Bordet and Gengou, *Ann. Inst. Past.*, xviii, 1904, 90.

³ *Jour. Phys.*, xxii, 1890, 739.

a firm coagulum, from which a perfectly clear serum is eventually separated.

It must be concluded, therefore, that calcium plays an important part in clotting. The controversy regarding the precise action of this salt initiated by Pekelharing,¹ has finally been settled by Hammarsten,² who has proved that it plays an important part during the first stage of this process. This deduction is based upon the observation that a calcium-free solution of fibrinogen may be made to coagulate by means of calcium-free thrombin, while the latter cannot be formed in the absence of soluble calcium salts. Again, oxalate plasma contains no fibrin ferment, but gives rise on cooling to an inactive precipitate in which active thrombin may be generated at any time by the addition of a soluble calcium salt. Obviously, therefore, the calcium serves the purpose of activating the prothrombin of the plasma, but when fully formed, the action of the thrombin cannot be hindered in any way by the precipitation of this salt.

Solutions of strontium citrate, sodium citrate or sodium metaphosphate also exert a retarding influence upon coagulation. Thus, if sodium citrate is added to blood in the presence of a calcium salt, a double salt of sodium-calcium-citrate is formed, and, as the calcium is retained in this union as a part of the acid radical, it cannot participate in the process of clotting. A similar result may be obtained with sodium fluorid in solutions of 3 parts of this salt to 1000 parts of blood. If thrombin is added to this mixture, coagulation sets in immediately. The calcium precipitates a portion of the protein, but invariably incites clotting if added in excess. To begin with, therefore, the calcium seems to be held as a fluorid in combination with a part of the protein, until its uncombined portion is enabled to manifest its characteristic action. Thus, the fluorid binds the calcium in the same manner as the oxalates.

Substances of Animal Origin.—The circulating blood of the mammals, and especially that of the dog, may be rendered non-coagulable by the procedure of peptonization which consists in injecting a solution of commercial peptone (Witte's) intravenously. To attain the aforesaid result, it is sufficient as a rule to use about 0.3 gram of peptone per kilo of the body weight. The blood of a peptonized animal remains fluid for hours after its withdrawal, and non-coagulable plasma may be obtained from it by the use of the centrifuge. Peptone solutions, however, are quite unable to produce this effect if the animal has been fed shortly before the injection or if they are added to fresh normal blood after it has been withdrawn from the body. It has also been noted that they do not retard the clotting very appreciably when introduced into the peritoneal cavity instead of directly into the blood-stream. This method of rendering the blood non-coagulable cannot be recommended for experiments upon the circula-

¹ Intern. Beiträge für Virchow's Festschrift, i, 1891.

² Zeitschr. für phys. Chemie, xxii, 1896, 333.

tion, because the peptone tends to cause a certain degree of vascular depression. The respiratory movements are quickened and the blood-pressure frequently drops to a very low level.

It is believed that this action of peptone is made possible by the liberation or formation of a substance which hinders coagulation, the so-called antithrombin.¹ As the latter is not a constituent of the peptone, it must be formed subsequent to its injection. Nolf² and others believe that it is produced in the liver, because the exclusion of this organ from the circulation destroys the aforesaid action of the peptone. Moreover, Delezenne³ has succeeded in producing an anti-coagulating agent by perfusing the excised liver with a peptone solution. It seems that this antibody is enabled to unfold its characteristic action by neutralizing a certain quantity of the fibrin ferment. It is also of interest to note that the peptone gives rise to a certain degree of resistance or immunity, because if a second injection is made a day later, it fails as a rule to render the blood non-coagulable. Extracts of crayfish or of mussels act in a somewhat similar manner.

Leech Extract and Snake Poisons.—A substance possessing a marked inhibitor power upon coagulation has been obtained by Haycraft⁴ from leeches. In its pure crystalline form it is known as hirudin. Although relatively resistant to high temperatures, its effectiveness may be materially lessened by heating it to 100° C. It behaves in general like a secondary albumose. When injected intravenously⁵ or when mixed with fresh blood after its removal from the body, it produces a rather lasting non-coagulability. Its action is said to depend upon the production of an antibody which, in accordance with the statements of Moravitz, regulates the formation of thrombin with quantitative precision. Pekelharing, on the other hand, has expressed the opinion that it prevents the liberation of those bodies upon which the production of the fibrin ferment depends. The latter view has recently been advocated by Bürker who emphasizes the fact that solutions of hirudin act preservatively upon the blood platelets.

Substances possessing a similar action have been found in *Ixodes ricinus*⁶ and in *Ankylostomum caninum*.⁷ In this connection attention should also be called to the biological peculiarity that the venoms of snakes may act either acceleratory or inhibitory. The poison of

¹ Fuld and Spiro, Hofmeister's Beiträge, v, 1904, or Moravitz, Archiv für klin. Med., lxxix, 1903-4.

² Arch. intern. de phys., ii, 1904-5.

³ Arch. de phys., viii, 1896, 655.

⁴ Arch. f. Exp. Path. u. Pharm., xviii, 1884, 209. It has been isolated by Franz (Archiv f. Exp. Path. u. Pharm., xlix). The leeches are dried, pulverized and extracted with normal saline solution. It suffices, however, to use only the head portions of these animals, because the active substance is contained in the buccal glands.

⁵ Use 10 to 20 cg. for 10 kg. of body weight in 10 to 20 c.c. of saline solution, and 1 cg. for each additional kilo of weight.

⁶ Sebatani, Arch. ital. de biol., xxxi, 1899, 375.

⁷ Loeb and Smith, C. Bact., xxxvii, 1904, 37.

the cobra, for example, inhibits the coagulation even in very minute doses in vivo as well as in vitro, because it prevents the conversion of the prothrombin into thrombin. The venoms of other snakes, for example, that of *pseudechis porphyrateus*,¹ behave in the same manner as tissue-extracts, but the question whether their action is identical with that of thrombin or of thrombokinase, has not been definitely decided.

Defibrination.—It is possible to hasten the formation of the fibrin by vigorously whipping the blood during its withdrawal with a rough stick of wood or with a bundle of fine wires. The shreds of fibrin then adhere to the wood, while the blood from which they have been removed remains fluid for an indefinite period of time. Obviously, this procedure causes a rapid destruction of those cellular elements from which the thrombokinase is derived. The fact that the fibrin may be separated in this way, is made use of at times in rendering certain inoperative aneurysms less dangerous to life. The blood contained in these saccular enlargements of the blood-vessels, is coagulated by the insertion of several long needles of steel. Acting as foreign bodies, these needles incite a deposition of fibrin in constantly increasing mass until the entire lumen of the tumor has been occluded.

Menstrual blood is commonly regarded as being non-coagulable. This belief is erroneous, because coagula are always present in the upper portion of the vagina. Only the fluid cruor mixed with mucus escapes. It is true, however, that the mucus retards the clotting, because it tends to smoothen the surface of this passage and to separate the individual masses of fibrin more widely from one another.

CHAPTER XX

THE TOTAL QUANTITY AND DISTRIBUTION OF THE BLOOD. LOSS OF BLOOD

Quantity of Blood.—It was formerly thought possible to determine the total amount of blood present in an animal by simply opening an artery and permitting the blood to escape until it ceased flowing. It must be evident, however, that this procedure is open to certain objections, because a considerable portion of the blood is always entrapped in the finer ramifications of the vascular system as well as in the central veins. Welker² has advocated the following method. A small amount of blood is withdrawn and diluted with saline solution in the proportion of 1:500. This mixture, designated as solution

¹ Martin, Jour. of Physiol., xxxii, 1905, 207.

² Zeitschr. für rat. Med., iv, 1858 (modified by Heidenhain).

a , is set aside in a receptacle of known capacity. The animal is then thoroughly bled, and its vascular channels washed out with normal saline. To avoid errors, the urinary and biliary bladders are removed. The different organs and tissues are then finely divided and thoroughly extracted with saline. This mixture (b) is subsequently diluted, until its color corresponds precisely to that of solution a when placed in the same kind of receptacle. If the volume of solution b is now divided by 500, the quotient indicates how many times the quantity of blood contained in solution a is contained in solution b .

The first attempt to determine the quantity of blood in a chemical manner has been made by Gréhant and Quinquaud.¹ Having ascertained the volume per cent. of oxygen in a given sample of blood, the animal was permitted to breathe a known volume of carbon monoxid. The total amount of CO was then determined and also the volume per cent. of O in a second sample of blood. The difference in the volume per cent. of O in the two samples corresponds to the volume per cent. of CO in the blood, because CO displaces an equal volume of O. The total quantity of blood is calculated according to the formula $\frac{V}{v} \times 100$; V stands for the total amount of CO absorbed by the blood, and v for the volume per cent. of CO, *i.e.*, for the number of cubic centimeters of this gas for each cubic centimeter of blood.

The method of Haldane and Smith² is based upon a similar principle. It depends upon the displacement of the oxygen from oxyhemoglobin by carbon monoxid. If a person is permitted to inhale a definite volume of CO, and if it is then found by means of a hemoglobinometer that $\frac{1}{2}$ of the hemoglobin of his blood has been saturated with this gas, it may be concluded that five times this amount is needed to charge all of his blood. In this way we ascertain what might be called the carbon monoxid capacity of the blood. We know that the amount of CO in CO-hemoglobin is identical with the amount of O contained in O-hemoglobin, and hence, the above value also indicates the oxygen capacity of the blood. Knowing the latter, the amount of hemoglobin present in the body can easily be ascertained, and knowing the percentage amount of the latter, the total volume of the circulating blood can thereupon be calculated.

To illustrate: A certain person exhibits the color of the 100 per cent. standard and possesses therefore a capacity of 18.5 c.c. of oxygen per 100 c.c. of blood. If, after the inhalation of 75 c.c. of carbonic oxid gas, his blood is found to be saturated with this gas to the extent of 15 per cent., an equal per cent. of the 18.5 c.c. must be present as carbon monoxid, namely, 2.7 c.c. Consequently, if 2.7 c.c. of carbon monoxid are present in 100 c.c. of blood after breathing 75 c.c. of this gas, it only remains to be determined how much additional gas must be inhaled in order to give the value of 18.5.

Thus, 2.7 c.c. per 100 c.c. of blood on inhalation of 75 c.c. of CO

1.0 c.c. per 100 c.c. of blood on inhalation of $\frac{75}{2.7}$ c.c. of CO

and 18.5 c.c. per 100 c.c. of blood on inhalation of $\frac{7.5 \times 18.5}{2.7}$ c.c. of CO

This implies that the total oxygen capacity is 500 c.c. As 18.5 c.c. of this amount are contained in 100 c.c. of blood, the total volume of blood which will carry 500 c.c. of the gas is: $\frac{500 \times 100}{18.5} = 2727$ c.c. The total weight of this mass of blood is ascertained by multiplying the volume with the specific gravity.

¹ Compt. rend., vii, 1883.

² Jour. of Physiol., xx, 1896, 295, and xxv, 1900, 497.

Quincke¹ attempted to estimate the blood volume from the change in the blood counts before and after transfusion. Lindemann² calculates the volume of the blood during transfusion with the help of the following factors: c , the cell percentage by volume of the blood introduced; b , the quantity of blood introduced, both being open to direct measurement; l , the cell percentage by volume of the patient's blood after the transfusion; x , the initial volume and a , the cell content of the initial volume. Then:

$$\begin{aligned} xa + bc &= l(x + b) \\ xa + bc &= lx + lb \\ xa - lx &= lb - bc \\ x(a - l) &= lb - bc \\ x &= \frac{lb - bc}{a - l} \end{aligned}$$

Thus: If the amount of blood transfused is 1500 c.c., the amount of blood previously withdrawn for tests 70 c.c., the cell volume before transfusion 13.7 per cent., the cell volume after transfusion 25.5 per cent. and the cell volume of the donor 40 per cent., then the blood volume of the patient amounts to:

$$\frac{40 \times 1500 - 25.5 \times 1500}{25.5 - 13.7} = 1843 \text{ c.c.} + 70 \text{ c.c.} = 1913 \text{ c.c.}$$

The circulating blood of the dog is estimated at about 7.7 per cent. of the body weight, in the cat and rabbit at 5 per cent. and in birds at 10 per cent. Similar values have been found by Bischoff³ and Weber and Lehmann⁴ in guillotined criminals. Based upon these early figures, the amount of blood present in an animal has always been calculated at one-thirteenth of the body weight. The experiments of Haldane and Smith, however, seem to prove that this figure is too high. Having obtained an average value of 0.49 per cent., these authors believe that the total quantity of blood in man equals only one-twentieth of the body weight. Thus, a man weighing 70 kg. possesses about 3684 grams of blood.

While the assumption that the quantity of blood preserves a direct relationship to the weight of the body, is a natural one to make, it should be remembered that we are not dealing with perfectly constant conditions, because the weight is subject to frequent changes. A deposition of fat, a greater development of the musculature, a transfer of lymph and other temporary and permanent alterations are prone to interfere with the establishment of such a relationship.

The Distribution of the Blood.—The blood having been ejected from the heart, is distributed to the different tissues and organs of the body in amounts commensurate with their activities. In general, it may be said that the tissues which form the framework of the body need a relatively small quantity, because, when fully grown, their upkeep and additional slight growth do not necessitate intense metabolic changes. Glandular tissues, on the other hand, need a

¹ Deutsch. Archiv für klin. Med., xx, 1877, 27.

² Jour. Am. Med. Assoc., lxx, 1918, 1210. Mention should also be made of the antitoxin method of von Behring (Münchener med. Wochenschr., lviii, 1911, 655).

³ Zeitschr. für Zoologie, vii, 1855 and ix, 1857.

⁴ Zeitschr. für physiolog. Chemie., Leipzig, 1853.

much larger quantity, because the production of a secretion or excretion always presupposes an abundant supply of fresh material. It should also be noted that an organ may receive a large amount of blood at any given time but may not retain much of it. Again, it may receive only a small quantity of blood, but hold a considerable portion of it in reserve as "residual blood." To illustrate: The intestine of a dog of medium weight is supplied with about 2.5 c.c. of blood in a second, or 150 c.c. in a minute. While this amount may seem to be unusually large, it should be remembered that the intestine of an animal of this kind weighs about 500 grams, so that the 150 c.c. of blood must actually be distributed to 500 grams of tissue substance. Hence, as only about 30 c.c. of blood are allotted to each 100 grams of intestine in a minute, this organ cannot be said to be very vascular. The reverse relationship exists in the case of the kidney. While the blood-supply of this organ is as copious as that of the intestine, its vascularity must be much greater, because its average weight is only 40 to 50 grams. In the succeeding table¹ the different organs of the dog have been arranged in accordance with the amounts of blood received by them per 100 grams of substance and per minute.

5 c.c. for the post. extremity	58 c.c. for the spleen
12 c.c. for the skeletal muscle	59 c.c. for the liver (venous)
20 c.c. for the head	84 c.c. for the liver (total supply)
21 c.c. for the stomach	136 c.c. for the brain
25 c.c. for the liver (arterial)	150 c.c. for the kidney
30 c.c. for the portal organs, combined	480 c.c. for the suprarenal body
31 c.c. for the intestine	560 c.c. for the thyroid gland

According to these results, the vascularity of the liver is surpassed by that of the brain, kidney, adrenal body and thyroid gland. But if considered solely from the standpoint of the blood-supply, the quantity allotted to this organ must be larger than that of any other, because as it receives about 7.0 c.c. in a second, its supply per minute amounts to more than 400 c.c. It will be seen, therefore, that the blood must complete the circuit through its channels once in about every three minutes. In accordance with the analyses of the respiratory air by Zuntz,² Krogh³ and Boothby,⁴ the lungs of man receive more than 3 liters of blood in a minute.

The data presented by Ranke⁵ tend to show that the blood is distributed at any one time as follows: one-fourth to the heart, lungs and central blood-vessels, one-fourth to the liver, one-fourth to the muscles and one-fourth to the remaining organs. These values have been obtained by measuring the amount of blood contained in the blood-

¹ Compiled in accordance with data presented by Burton-Opitz in *Pflüger's Archiv*, cxxix, 1908, and *Quarterly Jour. of Physiol.*, iv, 1911.

² *Zeitschr. für Balneologie*, iv, 1912.

³ *Skand. Archiv für Physiol.*, xxvii, 1912.

⁴ *Am. Jour. of Physiol.*, xxxvii, 1915.

⁵ *Die Blutverteilung und Thätigk. der Organe*, Leipzig, 1871.

vessels supplying the aforesaid organs after having previously ligated them at the same time. The tissues were then subjected to the chromometric test described previously.

Loss of Blood.—The blood escaping from a wound exhibits certain differences in color which are dependent upon differences in the location and extent or depth of the lesion. A bright red color signifies arterial bleeding and a dark red color a venous extravasation. In either case, the blood escapes in large volume, and, in arterial hemorrhage, under a considerable pressure. In capillary bleeding, on the other hand, the blood oozes out slowly as fine droplets which finally coalesce to form a flat coagulum. Its color is intermediate, provided, of course, that its oxygenation has not been interfered with by such conditions as venous stasis or arterial hyperemia. Hemorrhages are described as primary and secondary, the latter term being applied to those losses of blood which may occur after operations, in consequence of a belated or improper union of the parts. They are also classified as internal and external, according as to whether the blood escapes into a tissue or serous cavity, or actually reaches the surface of the body.

Repeated small hemorrhagic extravasations, or a single large hemorrhage, frequently result in a diminution in the volume of the circulating blood which must necessarily endanger the maintenance of proper dynamical conditions. This vascular depression may finally become so acute that the function of the different cells of the body is lost completely, that of the nervous centers being affected first. Hemorrhages may also prove fatal in a more direct way, in that the blood may find its way into a vital structure, and render it functionally useless. This is especially true of hemorrhages from the cerebral arteries into the adjoining nervous tissue. The complex of symptoms resulting therefrom, is known as apoplexy.

Small losses of blood are readily compensated for by a temporary diminution in the size of the blood-bed and a regeneration of the fluid and corpuscular elements lost. The fluid portion of the blood is quickly replaced by a transfer of lymph from the tissue spaces and lymphatic channels. The regeneration of its corpuscular constituents, however, requires a much longer time, because their formation depends upon the activity of the hematopoietic tissues which is gradual and cannot be made to surpass a certain maximal value. In case the loss of blood has been severe, it may not be possible to effect a compensation by ordinary physiological means, and an artificial restitution of the blood lost must be resorted to. This end is accomplished by the processes of *infusion* and *transfusion*.

The former procedure purposes to replace the fluid part of the blood directly by an artificial medium. A sterile 0.6 per cent. solution of sodium chlorid, heated to the temperature of the body, is usually employed. If the hemorrhage has been very severe and if the relaxation of the vascular system is extreme, a small amount of adrenalin should be added to the infusion liquid. As this agent constricts the blood-vessels, thereby lessening the size of the blood-bed, the blood pressure will

be more quickly restored than if the saline alone is used. For the same reason it has recently been advocated to raise the viscosity of this medium by the addition of gelatin.¹ The heart reacts much sooner if it is made to contract against a moderate peripheral resistance. Attention should also be called to the fact that the loss of pressure during the hemorrhage permits of the occurrence of certain reflexes which tend to prevent a fatal loss of blood by diminishing the force and frequency of the heart beat and by constricting the bleeding vessels at the seat of the injury.

The term transfusion is applied to the procedure purposing to displace or to replace a portion of the blood of an animal by the blood of another animal.² If accomplished by the direct method, an intimate connection is made between a blood-vessel of the donor and a vein of the recipient by means of a special cannula.³ The blood-vessels of the forearm are generally selected if the transfusion is to be performed upon man. Defibrinated blood has also been made use of, but this procedure is only permissible in animal experimentation, because the defibrination requires time and as the blood is subjected during this process to the influence of foreign bodies, it is difficult to retain it in an aseptic condition. Moreover, as the formation of fibrin is preceded by the production of certain agents which may in part remain uncombined, the danger of intravascular clotting of the blood of the recipient is not at all remote. The indirect method of transfusion necessitates the use of a receptacle in which the blood of the donor is retained for a brief period of time until permitted to flow into the veins of the recipient. This procedure is also open to serious objections, because, whatever precautions are taken, the danger of coagulation cannot be excluded with absolute certainty by the addition of an anticoagulating agent nor by the use of oiled and paraffined receptacles.

A method which is regarded with much favor at the present time is the so-called citrate method.⁴ Having applied a tourniquet to the arm of the donor, a cannula is inserted in one of the larger veins at the elbow (median cephalic). The blood is collected in a graduated cylinder containing a 2 per cent. solution of sodium citrate. If 50 c.c. of blood are to be obtained, 50 c.c. of the solution are taken so that a two per thousand mixture is effected. The blood is then rapidly transferred to a salvarsan apparatus containing 20 to 30 c.c. of a physiological solution of sodium chlorid, and is permitted to run into the punctured vein of the recipient by gravitation.

The direct transfer of blood from the donor to the patient was conceived at an early date,⁵ and has been practised repeatedly since the middle ages, either to replace blood lost by hemorrhage or to displace blood rendered useless by disease. It must be conceded, however, that the high hopes entertained for this procedure as a curative means have not been realized. In the first place, it is conceivable that the transfer of blood from the donor through an ordinary connecting cannula is liable to liberate the agents which subsequently cause intravascular clotting in the recipient. An unprotected cannula acts as a foreign body, and hence, great care must always be taken to keep the blood in relation with the normal lining of

¹ Bayliss, *Proc. Royal Soc., London*, 1917.

² Vogel and McCurdy, *Arch. Int. Med.*, Dec., 1913; also see: Robertson, *Jour. Exp. Med.*, xxvi, 1917, 221.

³ Esmarch (1877) used hydrostatic pressure to force defibrinated blood into the vein. In 1900 he advocated the use of normal saline solutions. The transfer of blood from one human being into another through the agency of a receptacle was first practised by Ziemssen (1892).

⁴ Carbat, *Jour. Am. Med. Assoc.*, lxi, 1915; Lewisohn, *ibid.*, lxxviii, 1917, 826, and Pemberton, *Surg., Gynec. and Obst.*, xxviii, 1919, 262.

⁵ Savonarola mentions the case of Pope Innocent VII who was bled and whose blood was injected into two young men. These men were bled later on and their blood passed into the veins of the Pope. The result, however, did not warrant a repetition of this procedure, because all three men died.

the blood-vessels. In recent years a number of cannulas¹ have been devised which make a direct anastomosis possible and obviate the danger of clotting. The second reason is intimately associated with the hemolytic property of the blood. As will be shown later, the body fluids of different animals contain certain agents which are prone to cause serious injury to the blood of the recipient. The constituents primarily involved are the red cells which are destroyed in varying numbers until a proper aëration of the tissues can no longer be effected.

Clearly, therefore, the blood of the donor should first be tested as to its hemolytic power before it can safely be introduced into the recipient. It may rightly be assumed that the blood of a widely divergent species is not at all suitable for transfusion, because its properties would most likely be very unlike those of the blood of the recipient. For similar reasons it may be concluded that the blood of an animal that is closely related to the recipient, is least prone to incite hemolysis. Thus, transfusions upon human beings will prove less dangerous and promise better results if a near relative is selected as the donor.

¹ Carrel, *Med. Record*, lxxxii, 1912, 1013.

SECTION V

THE LYMPH

CHAPTER XXI

PROPERTIES AND FORMATION OF LYMPH

General Consideration.—The lymph forms a medium of interchange between the blood and the tissues. This is made necessary by the fact that the blood does not come in actual contact with the cells, but remains separated from them by the lining of the capillaries. It thus plays the part of a middleman, and carries nutritive material to the cells in exchange for the products of their metabolism. It is true, however, that the importance of the lymph as a distributing agent varies in different tissues, because some of them are more vascular than others, and are equipped for this reason with a more intricate network of blood-capillaries. The individual cells are thus brought into closer relation with the blood-stream. Under less favorable conditions relatively large numbers of cells are grouped around a single blood channel, so that the nutrition of the outlying elements can only be effected by a correspondingly greater development of the lymphatic vessels and spaces. In fact, some tissues are free from blood-vessels, their nutrition being carried on by the lymph filling the delicate intercellular spaces permeating them. An arrangement of this kind is present in the central zone of the cornea through which the rays of light enter the eye. It need scarcely be mentioned that the presence of blood-capillaries in this particular structure would tend to hinder the refraction of the light rays.

The term lymph is generally applied to that part of the body fluid which is contained in the preformed lymphatic channels, while that part of it which bathes the individual cells, is designated as *tissue fluid*. This classification has some points in its favor, because the intercellular spaces are not always directly continuous with the larger central channels, but are at times separated from them by delicate membranous partitions. As the latter are only semipermeable, it usually happens that the composition of the tissue-fluid is slightly different from that of the *intravascular lymph*. Lymph, however, originates in all parts of the body and all types of lymphatic fluids contribute toward its formation. For this reason, it seems desirable to include under this heading also those liquids which are contained in the different serous spaces of the body, for example, in the pericardial, pleural and peritoneal cavities, and in the spaces of the

cerebrum, spinal cord, eyes, ears and joints. It should also be remembered that the lymph of the intestinal radicles assumes a milky appearance when much fat is being absorbed. It is then designated as chyle. The following fluids, therefore, may be included in this discussion:

Lymph	Intercellular.....	Tissue-fluid throughout the body
	Intravascular.....	Pericardial fluid
		Pleural fluid
		Peritoneal fluid
		Cerebrospinal liquid
		Aqueous humor
		Endo- and perilymph of the internal ear
		Lymph in the collecting channels
		Chyle

Properties of Lymph.—Large quantities of lymph may be collected by inserting a cannula into one of the large lymphatic channels, preferably the thoracic duct of the dog or cat. The latter arises in the upper part of the abdominal cavity and traverses the chest in close proximity to the descending aorta. It empties its contents into the left subclavian vein at its point of confluency with the external jugular vein

FIG. 119.—THORACIC DUCT.

(D) At its point of confluency with left subclavian vein (S); C, carotid artery; T, trachea; O, esophagus; LC, longus colli muscle; SA, scalenus anticus; L, lymphatic glands; E, ext. jugular vein.

FIG. 120.—THE DISTRIBUTION OF THE LYMPHATICS.

A, The domain of the thoracic duct (unshaded portion); B, right lymph duct; C, left cervical duct; D, right cervical duct.

vein. By following the latter into the aperture of the chest, a cannula may be inserted in this duct without rupturing the pleural mem-

branes. It is also possible to tap the cervical lymphatic duct which drains the different structures of the head. The thoracic duct, however, is to be preferred, because it collects the lymph from the largest part of the body, namely from the posterior extremities, the abdominal organs, and the entire left and lower right half of the thorax.

As the lymph is derived from the plasma of the blood, it may justly be assumed that its composition is very similar to that of the mother-fluid, but since the capillary wall really serves as a filter-like barrier, the plasma cannot pass through it as such but only in a much diluted form. For this reason, lymph is often designated as diluted plasma. If gathered during periods of fasting, it is as clear as water, and only slightly opalescent. It exhibits a yellowish green or yellowish gray hue. Its watery consistency is indicated by the fact that its specific gravity varies between 1.016 and 1.023, and its viscosity between 2400 and 3000. It is, therefore, only 1.7 times more viscous than distilled water at 37° C.¹ It possesses a salty taste, a faint odor, and an alkaline reaction, equaling 0.15–0.22 per cent. Na_2CO_3 . Soon after it leaves the duct, it changes into a homogeneous jelly and later on into a soft coagulum which embraces large numbers of white blood corpuscles of the type of the lymphocytes. These cells seem to be the carriers of the clotting agent, because their number bears a close relationship to the mass of the fibrin formed. The coagulation-time of lymph varies between 2.5 and 7 minutes, the average time being 4.5 minutes. It cannot be said, therefore, that it clots less speedily than blood (dog).

Lymph contains 3.6 to 5.7 per cent. of solids, the proteins consisting of fibrinogen, paraglobulin, and serum-albumin. When derived from the lymphatics of the liver, it presents an especially high percentage of albumin. Its fat content is small, namely 0.06 per cent. The salts comprise principally sodium chlorid and sodium carbonate. Diastatic and lipolytic ferments are also present. The following analytical data have been furnished by Munk.

Water.....	94.38–96.53 per cent.	
Solids.....	3.66– 5.62 per cent.	
Albumin.....	3.52– 3.54 per cent.	
Reducing substances.....	0.09– 0.10 per cent.	
Minerals		
NaCl.....	0.583 gram in 100 c.c.	} 0.87 per cent.
Na_2CO_3	0.217 gram in 100 c.c.	
K_2HPO_4	0.028 gram in 100 c.c.	
$\text{Ca}_3(\text{PO}_4)_2$	0.028 gram in 100 c.c.	
$\text{Mg}_3(\text{PO}_4)_2$	0.009 gram in 100 c.c.	
$\text{Fe}_3(\text{PO}_4)_2$	0.0025 gram in 100 c.c.	

If the animal is fed with food containing fat, the lymph traversing the thoracic duct eventually assumes a milky appearance. It is then known as chyle. This change becomes noticeable about 2 to 3 hours after the ingestion of this particular kind of food and is attributable to the absorption of globules of fat which gain the lymphatic system through its intestinal radicles, commonly designated as lacteals. By

¹ Burton-Opitz and Nemser, Am. Jour. of Physiol., xlv, 1917, 25.

inference it may therefore be concluded that the fat content of the lymph varies directly with the intensity of the absorption of this food-stuff. Thus, it is not uncommon to obtain as low a value as 0.06 per cent. during fasting, and values as high as 15 per cent. during periods of very active fat absorption. In this connection, attention should be called to the fact that the lymph does not aid in the absorption of the proteins, but plays a part, although rather insignificant, in the absorption of sugar. As will be shown later, these substances do not enter the lymph but are transferred in largest part into the blood-capillaries of the intestine.

The microscopic examination of clear lymph reveals numerous colorless corpuscles belonging to the group of the lymphocytes. Rather poor in cytoplasm these cells display a prominent nucleus. They arise in the lymphatic glands and nodes with which the lymph channels are beset and hence are always present in greater numbers in the lymph leaving these structures than in that entering them. A similar difference in the formed constituents of the lymph is noticeable in lymphoid tissues, such as the tonsils, thymus, spleen, and the different patches and glandular follicles of the intestine. This fact clearly shows that the organs just enumerated serve as places of origin for these cells, whence they are eventually flushed into the blood-stream to become one of the varieties of circulating white corpuscles.

The appearance of the different lymph-like fluids mentioned previously is very similar to that of the intravascular lymph. Normal *cerebrospinal fluid* is perfectly clear, colorless, slightly salty, and free from formed elements.¹ Its specific gravity varies between 1.002 and 1.008; its reaction is slightly alkaline. Its content in glucose (0.05 to 0.1 per cent.) corresponds to the amounts of sugar present in other serous fluids. Brief reference should also be made at this time to the fact that intracellular glycogen has been found to exist in the cells of the choroid plexus;² in fact, it appears that the cerebrospinal fluid is a true secretory product of this organ.³ This contention is based upon the observation that the formation of this fluid may be accelerated by extract of brain or retarded by extract of thyroid. The cerebrospinal liquor does not coagulate spontaneously, because it does not contain fibrinogen, but may be made to clot by the addition of small quantities of blood or lymph. This fact accounts for the peculiar phenomenon that this fluid frequently clots in the course of inflammatory conditions or after injuries to the nervous tissue. Obviously, lesions of this kind enable the elements of the blood to enter this fluid. The total quantity of cerebrospinal fluid is estimated at 60 to 150 c.c. of which 20 to 30 c.c. are contained in the ventricles.

¹ Anglada, *Le liquide céphalo-rachidien*, Paris, 1910 (Literature); also see: Plaut, Rehm and Schottmüller, *Leitf. zur Untersuchung der Zerebrosp. Flüssigkeit.*, Jena, 1913.

² Goldman, *Archiv für klin. Chir.*, ci, 1913.

³ Dixon and Halliburton, *Jour. of Physiol.*, xlvii, 1913, 215.

The data pertaining to the *humors of the eye*, and to the fluid in the endolymphatic and perilymphatic spaces of the internal ear, are not essentially different from those just given. The former have been proved to be true secretory products of the cells covering the ciliary body. Their function is to set up a pressure which keeps the different constituents of the eyeballs in a condition of tension and thus permits of the most perfect refraction of the light rays. The *pericardial fluid* is clear, yellowish in color, and sticky in character. It contains 2.3 to 4.5 per cent. of solids and does not clot spontaneously. Its content in salts (0.76 to 0.87 per cent.) is made up largely of sodium chlorid. The *synovial fluid* of the joints which, however, cannot be classified as a true transudate, possesses in general the same composition and characteristics as the general lymph, but contains in addition an appreciable amount of mucin.

The Sources of Lymph.—Volkman¹ has shown at an early date that the principal constituent of the body is water. Upon the basis of two-thirds of water and one-third of solids, an individual weighing 60 kilos may be said to contain 40 liters of water; and furthermore, since it has been established by Starling² that only about 100 c.c. of lymph are returned to the blood in the course of one hour (dog), a very large part of it must be held in the tissues. Only $\frac{1}{360}$ part of the total quantity of lymph reenters the blood in the time specified.

About 70 per cent. of the fluids of the body are contained in the muscles, bones and skin. This statement, however, does not imply that these structures give rise to a proportional amount of intravascular lymph; indeed, it has been found by Starling that the ductus thoracicus derives its contents largely from the abdominal organs which, under ordinary conditions, give lodgment to only about 7 per cent. of the total body-fluid. Practically no lymph is returned from the posterior extremities. It must be evident, therefore, that certain parts of the body contain considerable quantities of fluid, but permit only a small portion of it to escape into the central lymphatic channels. Others, again, are relatively poor in fluid, because they permit a free through flow. It is also true that an organ which gives rise to large quantities of intravascular lymph, generally furnishes a fluid possessing a high specific gravity. Thus, it has been ascertained that the lymph derived from the extremities is very poor in organic material, while that of the liver is rich in these complex substances. The lymph furnished by the other abdominal organs, is not quite so concentrated as the latter.

The Formation of Lymph.—Lymph is commonly regarded as diluted blood plasma, *i.e.*, as blood plasma which in its passage through the lining cells of the capillaries has lost some of its coarser constituents. Two theories are held regarding its formation. The oldest of these is the one advocated by Ludwig and his pupils, and modified more recently by Starling. It holds that lymph is formed in a purely

¹ Verh. d. sächs. Ges. der Wissensch., Leipzig, xxvi, 1874.

² Schäfer's Textbook of Physiology, i, 285, London, 1898.

mechanical way by the filtration of the blood plasma through the capillary wall. The second theory, propounded by Heidenhain and his pupils, maintains that the formation of lymph is not effected by filtration alone, but is also dependent upon osmosis and diffusion, and in addition upon a certain vital activity of the cells. To the latter the term of *vitalismus* has been applied. It must be clearly understood, however, that this designation does not allot to these cells metaphysical qualities, but only intends to imply that the formation of lymph is associated with certain microchemical and microphysical changes which at this time are still beyond scientific analysis.

In accordance with the pure filtration theory, it is held that a portion of the blood plasma is forced through the passive cells of the capillary wall as through a filter, *i.e.*, from a place of high pressure to a place of low pressure. The driving force is furnished in this case by the pressure prevailing in the blood-capillaries, while the area of low pressure is formed by the intercellular lymphatic spaces. As no other chemicophysical force is brought to bear upon this process, the quantity of the lymph formed must be directly proportional to the capillary pressure. This theory finds support in the composition of the lymph, because its inorganic constituents are practically the same as those of the blood plasma, while its content in protein is considerably less.

It also finds some support in certain observations to which attention has been called by Starling. Thus, it has been found that while the quantity of lymph is usually directly proportional to the height of the capillary pressure, it does not preserve this relationship at all times. This fact tends to show that a relatively low blood pressure may be associated with a very copious secretion, and vice versa. At all events, these results are not in accordance with the conditions necessary for filtration. This author also claims that the permeability of the capillary endothelium is not the same in all parts of the body. Thus, it is stated that the walls of the capillaries traversing connective tissue, offer a much greater resistance to the escaping lymph than those of the intestine and liver. The latter, in fact, are surprisingly permeable. In harmony with these structural and functional differences, it has been found that the lymph derived from the former is usually very dilute, while that from the aforesaid abdominal organs contains a very appreciable amount of proteins. The greatest possible permeability is shown by the capillaries of the liver, in which organ a copious transudation of concentrated lymph is frequently associated with very low pressures. In this connection it is of interest to note that the lining of the hepatic capillaries is in many places very incomplete, so that the blood is enabled to come into much closer contact with the liver-cells. For this reason, it cannot surprise us to find that a fluid which is injected into the arterial supply channels of this organ, frequently escapes into the spaces between the hepatic cells.

The influence which the capillary blood pressure possesses upon the production of lymph, may be more fully portrayed in the following manner. If the lymphatics of the liver are ligated, the largest part of the lymph traversing the thoracic duct, must of course be derived from the intestines. If the thoracic aorta is now obstructed, the flow of lymph ceases, owing to the diminished capillary pressure. Just the opposite effect, namely, a heightened driving force and an increased discharge of lymph, may be obtained by obstructing the portal vein. A similar experiment may be performed upon the liver itself. If the inferior vena cava is compressed centrally to the orifice of the hepatic vein, a pronounced diminution of the general blood pressure results which, however, is accompanied by an increase in the flow of the lymph from the thoracic duct. In view of the fact that the obstruction of the vena cava leads to an engorgement of the blood-vessels of the liver and a local rise in the capillary pressure, this result cannot surprise us, and especially not if it is noted that the occlusion of the hepatic vein remains without effect, provided that the lymphatics of this organ have been ligated beforehand. An augmentation of the capillary pressure of the posterior extremities may be produced in an easy way by blocking the venous return, but, curiously enough, this procedure does not materially increase the flow of lymph from this particular part of the body. Starling endeavors to unify these data by assuming that the height of the pressure plays a paramount rôle in the formation of lymph only in those organs in which the capillaries are very permeable, while in those organs in which they are relatively impermeable, other factors are brought into play.

The view of Heidenhain is based upon a number of facts which, however, do not deny that filtration plays a part but merely tend to prove that this factor is not the only one concerned in the formation of lymph. This author shows first of all that the different organs are quite unable to derive their entire supply of inorganic and organic material from lymph which is formed exclusively by filtration, because a quantity of fluid would be required to satisfy their needs which would be very much larger than that actually present in our body. For example, as 1.7 grams of CaO are contained in 1.0 kg. of cow's milk, the entire product for 24 hours would embrace about 42.5 grams of this substance. In order to render this amount available to the secretory cells of the mammary glands, 236 liters of lymph would be required, because this substance is normally present in a concentration of only 0.018 per cent. This discrepancy can only be explained by assuming that the filtration is associated with osmosis and diffusion which processes would naturally tend to augment that production of lymph which is had by pressure alone.

Heidenhain has also called attention to the fact that the increases in the flow of lymph are not always associated with rises in the capillary blood pressure. In testing the influence which the exclusion of different tissues and organs exerts upon the lymph flow, it was found

that the ligation of the hepatic vein is followed by an increased formation of lymph rich in proteins. This fact has been interpreted by this author as showing that the lining cells of the hepatic capillaries possess a true secretory power. Starling, on the other hand, came to the conclusion later on that it is due to the greater permeability of these channels occasioned by a certain structural deficiency of their lining. This diversity of opinion, however, does not lessen the weightiness of the observations of Heidenhain, because while it is possible to interpret this phenomenon in this way, a single exception of this kind does not materially weaken the sum total of the evidence presented.

Undoubtedly the most important facts brought forth by Heidenhain pertain to the augmentation of the lymph flow by means of substances which he has designated as lymphagogues. But, as these agents not only accelerate the production of lymph, but also give rise to lymph of a different concentration, they have been divided into lymphagogues of the first and second class. To the former group belong watery extracts of the dried muscles of crabs, crayfish and leeches, the products of certain bacteria, extracts of liver and intestine, peptone and egg albumin. In the second group must be placed all crystalline substances, such as sugar, sodium chlorid and other neutral salts.

On injecting a lymphagogue of the first class into the venous circulation, the flow of lymph is increased as much as six times the normal. This quantitative change is associated with a greater concentration and a lessened coagulability of the lymph, and may be obtained with very small amounts of the excitatory substance. The blood pressure, therefore, suffers no change whatever, and hence, this result cannot justly be attributed to an enhancement of the conditions of filtration. An even greater discharge of lymph may be obtained with the help of the lymphagogues of the second class, but naturally, as the introduction of these substances necessitates a solvent, it cannot be avoided that the plasma of the blood and the body-fluid are thereby rendered more watery. It is possible, however, to complete these injections without markedly increasing the general blood pressure, provided that the solution is permitted to enter slowly. It seems, therefore, that the careful introduction of moderate amounts of water as solvent cannot be seriously objected to, because it is not likely to augment the capillary pressure in a measure sufficient to be able to refer the increased flow of lymph to this cause.

Great importance has been attached to the fact that the flow of lymph continues for some time after death, and may even be heightened at this time by the injection of a lymphagogue. Strictly speaking, however, this phenomenon does not actually prove that lymph is formed after the blood has ceased to circulate, because it is quite probable that the tissue-fluid continues to seek the large lymphatics even after the capillary pressure has been destroyed. Stress has also been placed upon the fact that post-mortem lymph possesses a greater con-

centration than normal lymph. It must be admitted, however, that this change may be caused by a rapid influx of the "blood plasma" from the liver capillaries.

The view of Heidenhain, that the lymphagogues exert their characteristic action by stimulating the cells of the capillary walls to greater activity, has been objected to by Starling, upon the ground that the lymphagogues of the first class injure the lining cells of the blood-vessels, and especially those of the liver. Hence they permit a greater through flow of concentrated lymph simply by being more permeable. The lymphagogues of the second group are said by him to render the lymph hypertonic, thereby equipping it with a greater osmotic pressure. In consequence of this change the tissue-fluid is drawn into the larger lymphatics and eventually finds its way into the blood-stream. Priority, however, cannot be accorded to this statement, because Heidenhain has shown at an even earlier date that the lymph-driving properties of these substances are proportional to their osmotic power. Ascher¹ and his pupils regard the lymphagogues of the first class as liver-poisons which not only tend to increase the formation of lymph, but also accelerate the other activities of this organ. Thus, it has been demonstrated that chemical and morphological changes, such as a disappearance of the glycogen, result whenever these substances are injected. In a similar manner, Popoff² has shown that the introduction of peptone increases the flow of lymph from the thoracic duct, but does not augment the flow from other channels. This result is easily explained, because this extra quantity of lymph is derived principally from the intestine. It has also been noted that the peptone gives rise to a hyperemic condition of the portal blood-vessels which eventually culminates in hemorrhagic extravasations into the intestinal wall.

As the average student of physiology is largely concerned with the acquisition of definite fundamental facts and cannot be expected to display a keen interest in controversial discussions, it seems best not to debate this question further. Suffice to say, that we are in possession of certain agents which give rise to a greater formation of lymph without causing significant alterations in either the general or the local blood pressure. Clearly, if the dynamical conditions in the capillaries are permitted to remain the same, while at the same time a more copious discharge of lymph is obtained, it may justly be assumed that this result is dependent upon a greater activity of the lining cells of the capillaries. In accordance with the conception of Heidenhain, these cells may therefore be said to be equipped with true secretory powers. But even if the reader should feel inclined to favor the view that these phenomena do not necessitate the assumption of a vital activity on the part of the lining cells, the filtration theory would nevertheless have to be greatly modified, because we are still in a position to cite other data in opposition to it.

¹ Zeitschr. für Biologie, xxxii-xxvii, 1895-1906.

² Jour. of Physiol., xxv, 1899, 479.

It is a well-known fact that the stimulation of the chorda tympani nerve is followed by a dilatation of the blood-vessels of the submaxillary gland and a copious discharge of saliva. This effect is not obtained subsequent to the administration of atropin. Concerning the discharge of lymph, it has been found by Heidenhain and Cohnheim¹ that the excitation of this nerve causes no alteration, in spite of the fact that the vascularity of this organ is very much increased. Furthermore, it has been observed by Barcroft² that the water lost by the blood during its passage through this gland, enters not only the salivary ducts, but also finds its way in even greater quantities into the lymphatics. In this connection, it should also be mentioned that Ascher and his co-workers have proved that other organs, such as the thyroids, intestine, liver, and pancreas, give rise to much greater amounts of lymph whenever their activity is heightened, and that the lymph formed during these periods of increased metabolism is more concentrated. In explanation of these phenomena it is possible to submit three views, namely, (a) that any glandular activity leads to the production of certain substances which tend to stimulate the lining cells of the capillaries (Heidenhain), (b) that lymph may also be formed by the secretory cells of these glands (Ascher), and (c) that the complex molecules of the proteins, fats and carbohydrates are simplified so that the number of the particles in solution in the lymph is increased in harmony with the increase in the osmotic pressure of the latter (Starling).

The third view has also been offered by Starling and others in explanation of the fact that the intravascular lymph and tissue-fluid possess a greater molecular concentration than the blood.³ As has been stated previously, it is believed that the disintegration of the complex molecules renders the lymph hypertonic and that this catalytic change then leads to an influx of water into the lymphatics. On close examination, however, this explanation cannot be considered as a very good one, because it is known that the vascular walls are very permeable to water, and hence, it seems quite unlikely that the osmotic differences between the blood and the tissues can be maintained for any length of time. For this reason, it is safe to assume that the greater molecular concentration of the lymph can only be retained with the aid of some special activity of the lining cells of the capillaries.

In this connection, mention should also be made of the experiments of Heinecke and Megerstein⁴ which show that the sodium chlorid content of the blood-serum of nephritic rabbits is less than that of the ascitic fluid. Moreover, if this salt is ingested in larger amounts, the percentage of this salt increases in the serum as well as in the transu-

¹ Vorles. über allg. Pathologie, 2, Ausgabe, i, 1882, 493.

² Jour. of Physiol., xxv, 1899, 479.

³ Botazzi, Ergebn. der Physiol., vii, 1908, 310.

⁴ Archiv für klin. Med., xc, 1907, 101.

date, but in a more unmistakable manner in the latter. This result proves very clearly that the capillary wall possesses a certain selective power which enables it to keep the NaCl-content of the blood constant by facilitating the escape of the superfluous quantity of this salt. That the lining cells are also capable of furthering the escape of water has been demonstrated by the experiments of Carlson, Greer and Becht.¹ It seems that the lymph in the cervical ducts of the horse or dog may acquire a molecular concentration much below that of the blood; in fact, the difference may become so great at times that it cannot be explained upon the basis of ordinary hydrostatic laws. The secretory properties of the capillary lining cells are also proved in an indirect way by the fact that the cellular components of the salivary glands, kidneys and pancreas completely dominate the quantity and quality of their respective secretions. If this power is conceded to one group of cells, it would be difficult to deny it to other groups of cells. An impartial consideration of the evidence, therefore, must lead us to conclude that the formation of lymph is dependent upon (a) differences in pressure between the blood and lymph spaces, (b) differences in the concentration of the body fluids, and (c) true secretory properties on the part of the cells forming the capillary walls. Thus, the three factors engaged in this process are: filtration, diffusion and osmosis and a vital activity of the capillary cells.

The Factors Controlling the Flow of Lymph.—It has been stated above that the lymph is formed among the cells of the different tissues and that it moves from here with varying rapidity into the larger collecting channels, whence it again reaches the vascular system. The plasma thus temporarily diverted at the periphery into extravascular spaces, is eventually returned to the blood traversing the central circulatory system. A picture, the impressiveness of which can scarcely be surpassed, is presented at the point of confluency between the thoracic duct and the left subclavian vein. The clear lymph intermingles here with the dark venous blood in the manner of two rivers carrying varying amounts of sedimentous material. This picture is especially fascinating about two hours after the ingestion of fatty food, *i.e.*, after the lymph has assumed a milky appearance in consequence of its high molecular content in fat. The entire duct is then sharply outlined and may be followed to the receptaculum chyli and its tributary radicles upon the surfaces of the intestine. The discussion pertaining to this subject may be arranged as follows:

1. While the pressure under which the lymph is retained in the smallest channels amounts to only 10 to 15 mm. H₂O, it nevertheless decreases steadily in the direction from the tissues to the orifices of the main lymphatic ducts. Lymph is formed peripherally under a capillary blood pressure which may be reckoned at about 40 mm. Hg., while the pressure encountered in the central venous trunks amounts to — 5 mm. Hg.² Lymph, therefore, flows from a place of high pressure to a place of low pressure, but the decline is not equally rapid in all parts of the

¹ Am. Jour. of Physiol., xix, 1907, 360.

² Burton-Opitz, Am. Jour. of Physiol., ix, 1903, 198.

lymphatic system. No doubt, the greatest part of the original driving force is used up in its passage through the lining cells of the capillaries, because the pressure in the tissue spaces is very slight. Scarcely 10 mm. Hg are left for the return of the lymph from the tissue to the blood-stream.

2. The structure of the lymphatic tubules is very similar to that of the blood-capillaries. Their walls are composed of a single layer of elongated cells with sinuous outlines which are joined at their edges into delicate tubules. While the small lymphatic ducts are generally larger than the blood-capillaries, they do not retain a constant diameter throughout, because constrictions are formed here and there which impart a segmented or bead-like appearance to the entire channel. The diameter of the thoracic duct, for example, varies between 8 mm. and 4 mm. Of greatest importance to us at this time is the fact that these narrow places are usually beset with streamer-like valves which open only in the direction of the venous channels and close as soon as the pressure in the more central lymphatic rises above that in its tributaries. In this way, a backward flow of lymph is prevented.

3. The flow of lymph is also furthered by the contractions of the skeletal musculature. Under ordinary conditions, practically no lymph escapes from the resting limbs, while copious amounts of it are derived from the abdominal lymphatics.

FIG. 121.—CROSS-SECTION OF LYMPHATIC VESSEL TO SHOW ARRANGEMENT OF VALVES.

The muscles, however, are well supplied with fluid so that their contraction is immediately followed by an appreciable discharge of lymph. Quite naturally, as the lymphatics are equipped with valves, the pressure which is thus brought to bear upon their outside surfaces, must effect a quick onward rush of lymph in the direction of the more central ducts. The respiratory movements also facilitate the onward movement of lymph in an indirect way, because during inspiration the intraabdominal pressure is increased, while the intrathoracic pressure is decreased.

4. The importance of gravity as a factor favoring the flow of lymph varies with the position of the body. Under normal conditions, this force cannot exert an unfavorable influence upon dependent parts, for the same reason that it cannot hinder the flow of the blood. The lymphatics possess a certain degree of tonicity which tends to counteract the effects of gravity.

5. In amphibia, reptilia and birds, the flow of the lymph is also aided by lymph-hearts which contract rhythmically at the rate of about fifty beats in a minute. These pulsating saccules receive several lymphatics and give off a single tube which in most cases is directly connected with a blood-vessel. The orifices of the tributary tubules, as well as that of the central channel, are guarded by valves which insure a flow in the direction from the tissues toward the veins. In the frog, the pulsations of the lymph-hearts may be observed dorsally in the fore part of the body as well as next to the coccyx.

SECTION VI

RESISTANCE AND IMMUNITY

CHAPTER XXII

THE BLOOD AND LYMPH AS PROTECTIVE MECHANISMS¹

General Consideration.—The phenomena of resistance and immunity may justly be regarded as belonging to physiology, because the protection afforded an animal against toxic influences of all kinds, finds its origin in certain agents which are generated by the components of its tissues. In a practical way, however, the subject of immunity is more intimately related to bacteriology, and hence, it is intended to restrict the present discussion to the most essential general facts.

The body of an animal is protected in a certain measure against various poisonous substances, albuminous material, ferments, cellular products, and pathogenic bacteria and their derivatives. When fully developed, a resistance of this kind constitutes an immunity. Thus, an animal which cannot be affected by an ordinary dose of a certain toxic substance, is said to be immune against it. This resistance, however, may not be sufficient against larger doses of the same poison, nor against minimal doses of an unusually virulent toxin. Moreover, the degree of immunity may be varied by outside influences so that periods of resistance alternate with periods of susceptibility.

Immunity may be *partial* or *complete*, but the absolute type is rather uncommon. Thus, cold-blooded animals are often quite insusceptible to many of the bacteria which produce violent reactions in warm-blooded animals, while many of the latter are thoroughly protected against the infections which the lower forms are very prone to incur. As far as man is concerned, an immunity may be restricted to (a) all individuals, (b) certain races or tribes, (c) certain families, and (d) certain persons. For example, such diseases as Texas fever or hog cholera are not prevalent among mankind, while yellow fever and malaria do not usually attack the negroes of the West Indies. Quite similarly, certain families or individuals may possess a degree of resistance against tuberculosis which is not shown by others.

Like other biological characteristics, the power of resisting a specific pathogenic influence may be propagated from parent to off-

¹ A more detailed account will be found in Wassermann's "Immune sera, hemolysins, cytotoxins and precipitins," translated by Bolduan, New York, 1904.

spring, or may be acquired either by an accidental or an experimental infection. In the former instance, the immunity is said to be *natural* or inherited and, in the latter, *acquired*. The acquired type is specific in its nature, *i.e.*, it protects solely against a particular kind of toxic agent, and not against others. Thus, it is possible to develop a resistance against the bacillus of diphtheria, while at the same time the body remains open to infections by other germs, such as the bacillus of tetanus or typhoid. Moreover, while the inherited immunity is generally *permanent*, the acquired type is often only *temporary*, enabling the same germ to invade that animal a second time. It is true, however, that most of the infectious diseases, such as typhoid, diphtheria, yellow fever, small-pox, scarlet fever, and others, occur as a rule only once in the same individual. Immunity is also characterized as *general* and *local*, the former designation implying that the cells of the body as a whole are affected, and the latter, that solely a particular tissue is so favored. For example, it is a well-known fact that the Peyer's patches of the intestine do not offer favorable conditions for the growth of the typhoid bacillus if they have already served as the seat of a proliferation of this kind.

Active immunity is the resistance which is acquired by an animal in the course of an active immunization. Various methods are practised to render an animal immune in this manner, but all of them purpose to stimulate the tissues so that they take an active part in the development of the resistance. This end may be attained (*a*) with attenuated cultures, (*b*) with sublethal doses of virulent bacteria, (*c*) with dead bacteria, (*d*) with the products of the bacteria prepared from filtered cultures, and (*e*) by feeding the dead cultures.

Passive immunity is the resistance conferred upon an animal by introducing into its system certain immune agents which have been developed in another animal in the course of an active immunization. This procedure, which promises important therapeutic results, dates from the time of Behring (1890), who showed that the sera of animals immunized against the products of the tetanus or diphtheria bacillus, may be introduced into other animals with the result that the recipients are rendered resistant against these particular poisons. This type of immunity, therefore, is conferred upon an animal without it actively participating in this process of forming those elements which are responsible for the resistance. The sera employed in this process are known as antitoxic sera, and are said to contain antitoxins, or bodies which are specifically antagonistic to toxins.

In illustration of passive immunization might be mentioned the procedure usually followed in protecting human beings against the toxins of the diphtheria bacillus. The antitoxin concerned in this reaction is obtained in larger quantities with the help of young and vigorous horses. The systems of these animals is first accustomed to the diphtheria poison by the subcutaneous administration of small doses of diphtheria toxin. The doses are then gradually increased.

At the end of three or four months a quantity of blood is withdrawn from the jugular vein under antiseptic precautions, and is allowed to clot. Its serum is then treated in a special way and is finally standardized. Under favorable conditions, an animal yields from 250 to 800 units of antitoxin. For the prophylactic immunization of healthy individuals about 500 units are required, while in a therapeutic way, it may be administered in amounts ranging between 3000 and 20,000 units.

Causes of Immunity.—In general it may be stated that the immunity against microbic infection is dependent upon two processes, namely, upon the phagocytic power of the leukocytes, in the presence of opsonins (page 203), and secondly, upon the protecting influence of certain substances, known as antibodies. As perfectly definite histological elements have not been discovered as yet in the fluids of our body, these antibodies must be regarded as the products of precise chemical correlations, *i.e.*, as agents that have been developed in the course of physicochemical reactions between the cellular components of the tissues and the invading unit, or antigen. Thus, the effectiveness of an immunity must depend upon the quantity and quality of the antibodies which are formed in consequence of the stimulating action of the antigen.

The place of origin of these bodies has not been definitely ascertained. It is believed by some investigators that they are generated somewhere in the body in the course of tissue metabolism, while others hold that they are not independent elements but are derived from the leukocytes. If the latter view is accepted, which is that of the French school, the entire process of immunity constitutes merely a reaction which is secondary to phagocytosis. The facts brought forth by Ehrlich and his pupils, however, seem to contradict this conception. Thus, it has been found that the immune bodies exist preëminently in the blood, but their presence can only be established in a physiological way. In illustration of this statement it might be mentioned that the destructive power of sera upon bacteria is lessened by allowing them to stand, or by heating them to 56° C. It has also been observed repeatedly that immunized blood-serum is richer in globulin than normal serum.

Many physiological facts might be cited to prove that an animal is in actual possession of these antibodies and that it is equipped with them either at birth, or later on in the course of its life. It is also of interest to note that the formation of these bodies may be brought about not only with the aid of bacteria and their products, but also with the help of a number of different toxins of animal and vegetable origin. Ehrlich,¹ for example, has shown that specific antitoxins may be formed against the poisons of some of the higher plants. Similar protective substances have been obtained by Calmette² against the

¹ Deutsch. med. Wochenschr., 1891.

² Compt. rend., 1894.

venoms of snakes; moreover, Bordet,¹ as well as Belfanti and Carbone,² have established the fact that the serum of an animal into which the defibrinated blood of another species has been repeatedly injected, acquires the power of hemolyzing the red cells of this serum. Quite similarly, the repeated injection of spermatozoa³ may finally lead to the production of a blood-serum which acts destructively upon these elements. Reactions of varying specificity have also been obtained with ciliated epithelium, mucous tissue, pancreas, and kidney substance.

In general it may be said that the blood and tissue-fluids are capable of inciting any one of the following reactions:

- (a) A destruction of red corpuscles, hemolysis.
- (b) A destruction of other types of cells, cytolysis.
- (c) A destruction of bacterial cells, bacteriolysis.
- (d) An agglutination or clumping of cells of different kinds, inclusive of bacteria.
- (e) A precipitation of the cytoplasm.
- (f) A coagulation of the cellular contents.

The substances by means of which these reactions are brought about, are designated respectively as hemolysins, cytolysins, bacteriolysins, agglutinins, precipitins, and coagulins, but only the last four of these play a part in the production of that type of immunity which is specifically directed against pathogenic bacteria.

Nature of the Reaction.—Two theories are commonly held to explain bacterial immunity. Thus, it has been suggested by Roux, Buchner, and others that the antitoxic substances or antitoxins do not attack the toxins directly, but destroy them in an indirect way by rendering the body more resistant against them. In the second place, it has been proposed by Ehrlich, Behring and others that a specific interaction occurs between the antitoxin and the toxin in the nature of an ordinary chemical reaction. The evidence so far presented by different observers favors the latter view and, hence, it must be concluded that the union between the antitoxin and the toxin is dependent upon the presence of two distinct bodies which interact in accordance with the laws of valency. The chemical nature of this process is betrayed by the fact that concentrated solutions are more effective than dilute, and that it is accelerated by heat and retarded by cold.

In accordance with the accepted view pertaining to chemical neutralization, Ehrlich assumed that the molecule of the toxin consists of two separate groups or atoms, one of which unites with the antitoxin and binds it, while the other brings its specific action to bear upon the latter. The intermediary or anchoring portion is desig-

¹ Ann's de l'inst. Pasteur, 1896.

² Giron. della R. Acad. di Torino, 1898.

³ Metchnikoff, Ann's de l'inst. Pasteur, 1898, or Landsteiner, Centralbl. für Bakterienk., i, 1899, 25.

nated as "haptophore" and the poisonous portion as "toxophore." A similar view has been expressed by Arrhenius and Madsen,¹ who believe that the toxin possesses a weak chemical avidity for the antitoxin, the resulting reaction being similar to that occurring between a weak acid and base. The medium, therefore, would embrace uncombined toxin and antitoxin as well as the neutral product. It is quite impossible, however, to explain the phenomena of immunity in this simple manner. It has also been pointed out by Craw that the neutralization of the toxin is comparable to the action which takes place between absorbing membranes and certain dyestuffs. For example, if a piece of filter paper is placed in a solution of fuchsin, some of the dye adheres to the paper, the adhesion increasing with the concentration of the solution. Furthermore, if the piece of filter paper is first divided into several smaller ones which are then placed in the solution separately, the absorption will be more intense than that obtained with the help of the whole paper. It is also conceivable that the union of the antitoxin and toxin is not exclusively a chemical process, but is in part governed by physical laws.

An explanation regarding the relationship existing between the toxins and the cellular components of the body, was first made possible upon the basis of Ehrlich's theory pertaining to the nature of the protoplasmic molecule, published in 1885. When applied to the interaction between the antitoxin and the toxin, it is generally designated as the *side-chain theory*.² It is assumed that each protoplasmic molecule possesses a central core of protein upon which the specific activities of the cell depend. Branching out from this core we have a number of side-chains, or "receptors," by means of which the cell is brought into relation with the substances contained in the blood. An interchange of materials is effected through them which purposes the substitution of the waste products by newly acquired nutritive particles.

This process may be illustrated by the configuration given to the free and combined salicylic acid group. In this case, the benzol ring represents the radicle, and the COOH and OH the side-chains as follows:

¹ Zeitschr. für physik. Chem., 1902.

² Ehrlich, Collected Studies on Immunity, translated by Bolduan, New York, 1906.

In methyl salicylate, for example, the configuration is changed in this way:

In a corresponding manner, it has been suggested by Ehrlich that the toxins are capable of exerting their destructive action upon the body by becoming chemically bound to the cells through the intervention of the receptors of the latter. These are specific in their action and cease their function as soon as they have combined with the toxic substance. They are eventually broken down and destroyed. Thus, when the haptophore group of the toxin has been anchored to a receptoric side-chain, this particular feeler of the cell is of no further use and is cast off. The formation of the antitoxic substance depends upon the physiological reaction of the cell to this injury. In all probability the latter will endeavor to compensate for the loss of its receptors by the formation of new ones; indeed, the constant stimulation by the toxin will finally lead to an over-production of receptoric substance which, after its disconnection from the cell, is transformed into free circulating antitoxic substances. The latter represent the so-called antibodies which exert their protective action even in regions of the body far removed from their place of origin.

The side-chain theory of Ehrlich, therefore, furnishes a means for explaining the union between the cells of the animal and the toxins, as well as the formation of the antibodies. In the form just given it fails, however, to account for several phenomena frequently observed during experiments on immunity; for example, it has been noted that certain pathogenic bacteria against which the body is resistant, do not stimulate the formation of antibodies. Moreover, it has been ascertained a long time ago that the normal function of blood-serum to destroy certain pathogenic bacteria, may be wholly removed by subjecting it to a temperature of 56°C. , but a serum which has been rendered inactive in this way, may be reactivated by the addition of a small quantity of normal serum.

These and other facts have led to the assumption that the immune substances appear in the form of two, namely, as a thermolabile body, known as "alexin," and as a more stable body, called "sensitizing substance." Thus, it is believed that the bacteriolytic action of serum depends upon the combined action of these two substances. The first plays the part of the principal agent, and the second, that of the binder which renders the bacteria vulnerable. In the terminology

of Ehrlich, the alexin is known as "complement," and the sensitizing substance as "immune body." It is held by this investigator that the complement cannot enter into combination with the foreign substance, or antigen, unless it is attached to it by a mediator, the immune body. In accordance with an earlier suggestion pertaining to the construction of the toxin molecule, it is assumed further that the molecule of the immune body is composed of two groups or haptophores. In accordance with their degree of affinity for either the antigen or the complement, one of these groups is designated as "cytophile" and the other as "complementophile." On account of its "polarity," the immune body has been designated as the "amboceptor."

To summarize: the antigen (bacterium, blood cell, poison, etc.) cannot be affected by the complement (alexin or antibodies) unless it is prepared for this union by the amboceptor (immune body or sensitizer) which, on account of its polarity, is capable of becoming firmly anchored to it as well as to the complement. Thus, the interaction between the complement and the antigen is made possible only through the intervention of the amboceptor.

Anaphylaxis.—The term anaphylaxis (ana: against, phylaxis: protection) was first employed by Richet¹ in 1905 to indicate an increased

sensitiveness or susceptibility toward infective and other toxic materials. While studying the action of the poison derived from the sea anemone, he found that if a small dose of it, which produced no symptoms upon its first injection, was followed a week or two later by another small dose, the animal became ill and usually died. Thus, the most acute symptoms may follow a dosage which in normal animals produces no effects at all. Inasmuch as a summation effect cannot be held responsible for this phenomenon, because the interval of time between the two successive injections is altogether too long, it must be concluded that this condition of very pronounced susceptibility is developed at some time in the course of this reaction. This deduction implies that certain bodies are called into existence which eventually produce an acute toxic state. These bodies, however, exhibit a marked specificity, and may be passively transferred to other animals. It has been shown in guinea-pigs that they may be transmitted by the female to her offspring.

This susceptibility was recognized in reality before Richet applied to it the name of anaphylaxis. Thus, it had been observed that the administration of antitoxins is followed at times by most severe symptoms, giving rise to what Pirquet and Shick² have called serum

FIG. 122.—DIAGRAM ILLUSTRATING INTERACTION BETWEEN COMPLEMENT C AND ANTIGEN A.

Am, amboceptor; Cy, cytophile and Co, complementophile part of amboceptor.

¹ Soc. Biol., lxiv, 1908, 847, and Ann. Inst. Pasteur, xxi, 1907.

² Wiener klin. Wochenschr., 1902, No. 26.

sickness. Arthus,¹ moreover, had proved that a second injection of horse serum into rabbits frequently causes a very intense reaction, so much so that this formerly perfectly harmless procedure becomes distinctly injurious. Quite similarly, it had been observed that a tuberculous person is hypersensitive to tuberculin and that injections of cocain eventually give rise to an increased susceptibility, as evinced by undue rises in the body temperature.² A similar hypersensitiveness follows the repeated administration of apomorphin.³ Anaphylaxis, therefore, may be active and passive, because it is possible to render an animal anaphylactic by these injections and also to transfer this state from a sensitized to a normal animal. The latter process requires the injection of the serum of an anaphylactic animal which is then followed, say 24 hours later, by an injection of the antigen originally used to produce this condition in the first animal.

Numerous theories have been advanced to explain anaphylaxis. In general it may be said to be a reaction between the antigen and the specific antibody. In the same way as antibodies are developed after a definite period of incubation, a certain antigen may eventually give rise to anaphylactic bodies, such as toxogenin (Richet) anaphylactin or sensibilin. This complex formed by the antigen and antibody becomes poisonous in the course of this reaction, but it may also be true that the reaction affects the medium (blood-serum) in such a way that it assumes toxic properties.

¹ Soc. biolog., lv, 1903, 817.

² Adnico, Arch. ital. de biol., xx, 1894.

³ Richet, Soc. biolog., lviii, 1905, 955.

PART III

THE CIRCULATION OF THE BLOOD

SECTION VII

THE MECHANICS OF THE HEART

CHAPTER XXIII

A COMPARATIVE STUDY OF THE CIRCULATORY SYSTEM

General Arrangement of the Vascular System.—In its simplest form the circulatory system consists of two parts, namely, a fluid and a circular tube, the caliber of which is greatly increased at one point to represent the pumping mechanism, or heart. The latter first appears in the form of a simple bulbular enlargement of the general vascular channel and finds its origin in the deposition of large numbers of muscle cells possessing automatic properties. This enables the walls of this organ to contract at intervals and to place the fluid within under a higher pressure than that prevailing in the tubes without. In consequence of this difference in pressure, the fluid is forced through orifices (*A*) and (*B*) into the distal channel (*C*), but as every phase of contraction of the musculature must necessarily be followed by a phase of relaxation, the fall in pressure then resulting within the heart must permit the fluid to return into the central cavity (*H*).

A simple arrangement of this kind, however, is not adapted for anything dynamically more perfect than an oscillatory to and fro motion of the fluid. A true circular motion can only be imparted to the fluid within this system by guarding the aforesaid orifices (*A* and *B*) of the heart (*H*) by valves which open only in the direction of the flow. These valves having been put in their proper places, the contraction of the cardiac musculature now forces the fluid across the yielding valve flap (*A*) into the distal channel (*C*), but is unable to drive it through the opposite orifice (*B*), because this valve closes immediately upon the first increase in the central pressure. A moment thereafter, however, when the relaxation of the cardiac musculature has led to the establishment of a lower central pressure, the valve at (*B*) is opened, allowing the fluid to reënter the central compartment. Inasmuch

as valve (A) is firmly closed at this time, a definite direction of flow is now imparted to the fluid. It leaves the heart (H) through the arterial orifice (A) and cannot return to this organ until it has traversed the entire tube (C).

The channel which conveys the blood away from the heart is known as an artery, while the one returning the blood to this organ is called a vein.¹ In a true circulatory system these two divisions are joined by a multitude of fine tubules, designated as capillaries, so that the entire vascular system is really composed of three parts, namely of arteries, capillaries, and veins. In accordance with certain structural peculiarities, these channels may be subdivided further so that in final analysis the circulatory system consists of arteries, arterioles, arterial capillaries, capillaries proper, venous capillaries, venules, and veins. The central arterial tube is commonly spoken of as the aorta, and the central collecting channel as the vena cava.

FIG. 123.—SCHEMA OF SIMPLE CIRCULATORY SYSTEM.

I, phase of contraction; II, phase of relaxation of heart; A and B, valves guarding cardiac orifices; D, arteries; C, capillaries; E, veins.

The Circulatory System in the Lower Animals.—In the lowest forms the nutrition of the outlying colonies of cells is effected by progressive and oscillatory streams which are brought into existence by differences in pressure as well as by the processes of diffusion and osmosis. In the highest animals, on the other hand, these simple movements give way eventually to a complex roundabout motion of the body fluid, but this end is not attained until the circulatory mechanism has passed through several intermediary stages of development.

In order to be able to follow these changes more closely, it seems advisable to initiate this discussion with a study of the conditions existing in such forms as the *sponges* which may be said to possess a circulation of the most elementary kind. We find here that the water enters through numerous pores of the derma and is then returned to the surrounding medium by way of the central canal and the osculum. The power necessary to produce this flow is furnished by the cilia with which the aforesaid passage is beset. The higher *coelenterates* are in possession of an alimentary canal, the smaller recesses of which extend far into the substance of their bodies. In this way, these saccular extensions are enabled to serve

¹ For this reason, the pulmonary artery is known as an artery, although it contains venous blood, and the pulmonary vein as a vein, in spite of the fact that it contains freshly aerated blood.

as intermediary agents between the distant cells and the nutritive material in the alimentary passage. In the medusa well-marked gastrovascular streams may be observed. The lower *vermes* exhibit an arrangement very similar to that found in the coelenterates. In the slightly higher forms, however, the alimentary tract is completely separated from the general body cavity, so that the gastric prolongations are enabled to assume the function of true circulatory channels. The fluid within them is albuminous in character, and is moved from place to place by differences in pressure produced by the general movements of the body. In some annelids, the circulatory system is fully differentiated and consists of a dorsal and a ventral tube which are connected with one another by several branches. As the latter, as well as the adjoining segments of the dorsal tube, are automatically active, these forms may be said to be in possession of a real heart which, however, presents a most rudimentary structure. Its most essential characteristic is its tubular shape. In *Arenicola*, the main cardiac cavity is constricted at one point so that the cardiac tube as a whole appears as two distinct compartments.

Similar differences are to be noted among the *vertebrates*. *Amphioxus*, for example, does not possess a distinct heart, a portion of its posterior aorta being equipped with automatic power. It should be remembered, however, that this animal presents the first indications of a portal circuit, because the dorsal aorta gives off certain branches to the intestine, from which organ the blood is then collected by a single tube, which is known as the portal vein. Having traversed the capillaries of the liver, the blood is eventually returned into the ventral aorta.

In the lower animals, the power of rhythmic activity extends over relatively long segments of the dorsal and lateral blood-vessels; but in the fishes the heart loses its diffuse tubular character, and the power of contraction becomes restricted to a particular area of the vascular system. These animals are in possession of a cardiac mechanism which occupies the ventral extent of the body-cavity and presents a structure very similar to that found in the higher animals. It is protected on all sides by a membrane which is reflected from its base to form a pouch, the so-called pericardial sac. The organ, as a whole, is composed of two compartments, an antechamber or auricle, and a main chamber or ventricle. Moreover, as the veins do not unite with the auricle as separate tubes, but become confluent, a vestibular chamber is formed which is commonly designated as the sinus venosus. Quite similarly, the aorta does not arise from the ventricle itself, but from an appendage,

FIG 124.—DIAGRAM TO SHOW THE COURSE OF THE BLOOD THROUGH THE FISH HEART.

SV, sinus venosus; A, auricle; V, ventricle; BA, bulbus arteriosus; A, aorta with (C) arteries to gill plates.

known as the conus arteriosus. All these different parts of the heart possess contractile powers, their action being coördinated in such a manner that the sinus contracts first, the auricle next and the ventricle and conus last of all. The blood traverses the chambers of the heart in the same direction. An oscillatory flow is made impossible by: (a) the proper sequence of contraction of the different segments of the heart and (b) the fact that the cardiac orifices are guarded by valves which open only in the direction from sinus to ventricle.

In accordance with the force which the different parts of the heart must develop in order to propel the blood, the ventricle contains a much greater amount of muscle tissue than the auricle or sinus. It must be remembered that the ventricle produces the pressure which is necessary to drive the blood through the entire vascular system. In accomplishing this end it must overcome the relatively high resistance prevailing in the peripheral blood-vessels. The sinus and auricle, on the other hand, pump the blood merely into the adjoining ventricle and, as this transfer is effected at a time when the latter is in a condition of rest, the ante-chambers need not develop anything more than very moderate degrees of pressure.

FIG. 125.—DIAGRAM TO SHOW THE COURSE OF THE BLOOD THROUGH THE AMPHIBIAN HEART.

SV, sinus venosus; RA, right auricle; LA, left auricle; V, ventricle; BA, bulbus arteriosus; A, aorta; PA, pulmonary arteries; PV, pulmonary veins. The striated portion contains venous blood, the dotted portion mixed blood, and the clear space, arterial blood.

to the dorsal aorta by way of the efferent vessels. In this way, only a part of the blood discharged by the heart finds its way into the gills, where it is aerated and is distributed subsequently to all parts of the body. It is returned to the heart thoroughly charged with carbon dioxid. The fourth subclass of the fishes, the Dipnoi, present rather complicated conditions, because they are equipped with lungs as well as with gills and hence, are in possession of a pulmonary and a gill-circuit.

The heart of the amphibians is situated in the fore part of the body ventrally to the first vertebræ, and consists of a sinus venosus, two auricles, and a ventricle with its bulbus arteriosus. The blood which

A peculiar modification of the circulatory system is found in fish. Inasmuch as the respiratory interchange in these animals is effected by means of the gills, this particular circuit is most highly developed, while the lungs with their pulmonary system of blood-vessels are, of course, absent. The circulation of the gills is made possible by a number of afferent branches which are given off from the ventral aorta and lead to the different gill-plates. From here the blood is conveyed

is returned from the system, flows into the right auricle, while the blood which has just been aerated in the lungs, enters the left auricle. When these parts contract, both types of blood are simultaneously forced into the ventricular cavity, where they must intermingle somewhat, because they are not kept apart by partitions. It must be emphasized, however, that a thorough mixture of the aerated with the venous blood cannot take place, because the interval between the auricular and ventricular contractions is extremely brief, and because the ventricular wall contains numerous recesses, in which at least a part of the venous and oxygenated types of blood finds separate lodgment. It is only natural to suppose that these types of blood will be forced into those parts of the ventricle which lie directly below their respective auricular orifices. It is also true that the venous blood reaches the conus arteriosus ahead of the oxygenated, because the right expanse of the ventricular cavity lies nearest this structure. Moreover, as the resistance in the pulmonary circuit is less than that in the systemic blood-vessels, the first gush of ventricular blood, venous in character, must find its way into the lungs by way of the pulmonary artery; while the aerated portion following it must necessarily be diverted into the peripheral channels. A special system of blood-vessels for the musculature of the heart is not present in amphibians. These animals, however, are in possession of a hepatic portal system and a peculiar renal portal system. The latter modification of the vascular mechanism finds its origin in the double blood-supply of the amphibian kidney. It will be remembered that its glomeruli receive their blood from the aorta directly, while the remaining portions of the urinary tubules are supplied by the renal portal vein.

The heart of the reptiles resembles that of the amphibians in several particulars. It also consists of a sinus, two auricles, and a ventricle. A two-lipped valve is situated in the sino-auricular orifice and a right and left semilunar valve in the corresponding auriculo-ventricular openings. The ventricle, from which the aorta and pulmonary artery emerge separately, is divided into two compartments by a muscular septum. The separation is complete in the crocodiles, but incomplete in the snakes, lizards, and turtles. In the animals named last, the tendency is to keep the venous blood separated from

FIG. 126.—DIAGRAM TO SHOW THE COURSE OF THE BLOOD THROUGH THE REPTILIAN HEART.

SV, sinus venosus; RA, right auricle; LA, left auricle; V, ventricle incompletely divided by a septum; A, aorta; PA, pulmonary arteries; PV, pulmonary vein. The striated portion contains venous blood, the non-striated arterial blood.

the aerated, the former being held in the compartment to the right, and the latter largely in the space to the left of this septum. During the contraction of the ventricle, the edges of the septal flaps are brought together so that the largest amount of the venous blood is forced into the pulmonary artery, while the oxygenated blood is diverted chiefly into the aorta. But while definite provision has been made in these animals to prevent a complete mixture of the venous with the aerated blood, a certain degree of intermingling is still possible in several places outside the heart. Excepting certain fish, the reptilian heart is the first to exhibit a system of blood-vessels for the nutrition of the cardiac

FIG. 127.—DIAGRAM TO SHOW THE COURSE OF THE BLOOD THROUGH THE HEART OF BIRDS.

PC, post. cavæ; RA, right auricle; LA, left auricle; RV, right ventricle; LV, left ventricle; PA, pulmonary artery; PV, pulmonary vein; A, aorta.

musculature. The hepatic portal is associated with a renal portal system.

The heart of birds possesses four chambers, namely two auricles and two ventricles. A distinct vestibular portion is not present. The blood is returned from the tissues by the right and left post. cavæ. It enters the right auricle and then the right ventricle, whence it is conveyed to the lungs through the pulmonary artery. Four pulmonary veins conduct it from here to the left auricle and left ventricle, whence it again attains the peripheral tissues by way of the aorta and its branches. Thus, for the first time, the aerated blood is completely separated from the venous blood by a longitudinal septum which divides the heart into a right and a left side. Each side in turn embraces an antechamber, or auricle, and a main chamber, or ventricle. The auriculoventricular orifices are guarded by membranous valve

flaps, the right being large and muscular. The aortic and pulmonary orifices are beset with three cup-shaped valve-flaps. Owing to the functional importance of the wings and the corresponding massiveness of the pectoral muscles, the arteries supplying these parts are very large in caliber. Moreover, in agreement with the position of the legs, the femoral blood-vessels are found far forward in the body.

The Circulatory System in Mammals.—In mammals, the heart is divided into a right and left half and each half in turn into an antechamber, or auricle, and a main chamber, or ventricle. The blood which is returned from the tissues, enters the right auricle by way of the superior and inferior venæ cavæ, while the blood from the lungs is conducted into the left auricle by way of the pulmonary veins. Two distributing channels leave the heart, namely, the pulmonary

artery and the aorta. The former conveys the blood from the right ventricle to the lungs, and the latter from the left ventricle to all parts of the body.

If the multitude of blood-vessels constituting the different divisions of the circulatory system are taken and moulded into single channels, a system of tubes is formed such as is represented in the adjoining schema (Fig. 128). In studying this diagram more closely, we find that a droplet of blood leaving the left ventricle first enters the central arterial trunk, or aorta, whence it escapes into either the blood-vessels of the head or those of the trunk and lower extremities. In either case, it must first traverse the arteries, then the arterioles and finally, the capillaries. Having attained the other side of these extremely fine tubules, it enters the venules and then the veins to be eventually conveyed into the right auricle. The venous trunks in the vicinity of the heart are designated as the superior and inferior cava respectively.

This extensive system of blood-vessels which supplies all the tissues of the body with the exception of the lungs, constitutes the *greater, or systemic circuit*. It embraces two specialized smaller divisions, namely, the *coronary and portal circuits*. The former arises from the root of the aorta as the coronary artery and ends in the right auricle as the coronary vein or sinus. The coronary blood-vessels have to do solely with the nutrition of the heart. The portal circuit begins with the arteries supplying the so-called portal organs, namely, the spleen, pancreas, liver, stomach, and intestine. Having traversed the different capillary networks of these organs, the blood is collected by a single channel, known as the portal vein, and is then conducted to the liver, whence the hepatic veins convey it into the inferior vena cava. The portal circuit, therefore, is concerned chiefly with the processes of digestion and absorption.

FIG. 128.—SCHEMA OF THE CIRCULATION.

A, aorta; Ar, arteries; Art, arterioles; AC, arterial capillaries; C, capillaries; VC, venous capillaries; Ve, venules, Ve, veins; VCS, vena cava superior; VCJ, vena cava inferior; RA, right auricle; RV, right ventricle; LA, left auricle; LV, left ventricle; 1, tricuspid valve; 2, mitral valve; 3, pulmonary semil. valve; 4, aortic semil. valve; PA, pulmonary artery; L, lungs; PV, pulmonary veins; PO, portal organs; PV, portal vein; HA, hepatic artery; Li, liver; HV, hepatic vein.

The second principal division of the circulatory system is formed by the *lesser or pulmonary circuit*. It consists of the pulmonary artery and its branches which conduct the blood from the right ventricle into the capillaries of the lungs, and of the pulmonary veins which collect the aerated blood and return it into the left auricle. Thus, while every drop of blood is forced to traverse the greater and lesser circuits successively, the course which it may pursue is not restricted to one and the same channel, because it may pass either into the capillaries of the head or into those of the heart, portal organs and posterior extremities. In other words, a large number of shorter and longer paths are open to it.

In perfect agreement with the circulation in the lower forms, the blood of the mammal is made to flow in the direction indicated, because the contraction of the auricles antecedes that of the ventricles by a definite period of time, and because the circulatory channel is beset with valves which open only in one particular direction. As far as the second factor is concerned, it should be stated at this time that there are three sets of valves to be considered, namely: (a) the auriculo-ventricular which guard the openings between the auricles and ventricles, (b) the semilunar which are situated in the orifices of the aorta and pulmonary artery, and (c) numerous venous valves which are placed as a rule at the points of confluency of small and large veins. The first set of valves comprises the tricuspid and mitral, the former being placed in the right and the latter in the left orifice. Both open downward into the cavities of the ventricles. The second set consists of the pulmonary and aortic semilunar valves. Their flaps yield outward, *i.e.*, in a direction away from the ventricles. The venous valves open only toward the heart.

The Circulatory System During Fetal Life.—The circulatory system of the adult human being finds its origin in the system which is present during the last months of intra-uterine life. The complete separation of the young from the mother effected at birth, necessitates first of all the presence of a heart that is capable of developing an adequate driving force, and secondly, several very definite alterations in the distribution of certain blood-vessels which insure a perfect continuity of the vascular channels. It should be emphasized, however, that the changes effected at birth, are not the only ones to which the circulation of the human embryo is subject to. Thus, it has been established that the early vitelline system which is fully developed during the third week, is modified several times to meet new conditions, and its shortcomings are soon compensated for by the formation of the allantoic vessels which are specialized further into the placental circulation. The following peculiarities are evident during the last months of gestation. The blood spaces of the placenta which lie in contact with the enormously enlarged capillaries of the uterus, unite eventually to form two blood-vessels, commonly known as the umbilical artery and vein. The latter conveys the blood from the

placenta to the fetus. Very soon after it enters the fetus through the umbilical perforation, it divides into two channels, one of which unites directly with the inferior vena cava, and the other with the portal vein in the immediate vicinity of the liver. The portal branch

FIG. 129.—THE FETAL CIRCULATION.

P, placenta; *UV*, umbilical vein carries oxygenated blood and unites with the vena cava inferior (*JVC*) and portal vein (*PV*). This blood mixes with the venous blood and enters the right atrium (*RA*) being here diverted largely through the foramen ovale into the left auricle (*LA*). From here it passes into the left ventricle (*LV*), aorta (*A*) and either into head circuit or abdominal aorta (*AA*). Here it may be diverted into the portal organs (*PO*) or continue onward into the common iliac (*CJA*), external iliac (*EJA*) or hypogastric arteries (*HA*). In the latter case the blood again reaches the placenta by way of the umbilical arteries (*UA*). The blood from the head enters the superior vena cava (*SVC*) and right auricle (*RA*), where it is diverted into the right ventricle (*RV*) and pulmonary artery (*PA*). From here it passes chiefly through the ductus arteriosus (*DA*) into the aorta. A small portion of it traverses the lungs proper (*L*) to be returned to the left auricle (*LA*) by way of the pulmonary vein (*PV*). The striated vessels contain venous blood and the dotted vessels, mixed blood.

is known as the ductus venosus. Whichever course the placental blood selects, it eventually reaches the right auricle. It is to be noted, however, that it is immediately mixed with the blood of the inferior

cava which in all probability is fully loaded with the waste products of the fetal tissues.

On account of the peculiar position of the orifice of the inferior cava and the presence of a lip-like membrane, known as the Eustachian valve, the blood entering the right auricle is immediately directed through an opening in the interauricular septum into the cavity of the left auricle. This orifice which thus grants a free passage to a portion of the venous blood into the arterial side of the heart, is called the foramen ovale. Under normal conditions this defect is closed very shortly after birth, its place being taken by a tense fibrous membrane which forever thereafter remains sharply differentiated from the much thicker muscular portion of this septum. In certain infants, however, it does not become patent until several weeks after birth; in fact, in some it never becomes completely impervious. The venous blood then continues to intermingle with the arterial and the more so, the larger the size of the opening remaining. In indication of the poor aeration of the tissues resulting in consequence of this condition, the skin and mucous membranes of these children retain a bluish appearance.

From the left auricle, the blood passes into the left ventricle and from here into the aorta. If it is now diverted into the blood-vessels of the head, it eventually reaches the right auricle by way of the superior vena cava. Peculiarly enough, the stream from this blood-vessel is directed in such a way that it flows directly through the right auriculoventricular opening into the ventricle of the same side without seriously interfering with the cross-current through the foramen ovale. The pulmonary artery then conducts the blood into the lungs, but as these organs are inactive and are merely a slowly growing mass of tissue, they do not require much blood. For this reason, by far the largest quantity of the blood of the pulmonary artery is not distributed to the lungs at all, but escapes into the aorta by way of a special channel, commonly called the ductus arteriosus. Only an insignificant portion of the blood of the pulmonary artery actually reaches the capillaries of the lungs, whence it again attains the left auricle by way of the pulmonary veins. This blood, of course, serves solely the purpose of supplying nutritive material to the growing lung tissue.

A droplet of blood may pursue the course just outlined a number of times, but it may also happen that it is forced into the posterior parts of the body, *i.e.*, into the portal circuit or into the blood-vessels of the legs, and eventually regain the heart by way of the inferior cava. Last of all, it may leave the fetus altogether and return to the placenta by way of the hypogastric branches and the umbilical artery. Clearly, therefore, the paths which a drop of blood may follow, are even more numerous and diverse in the fetus than they are in the adult. It may be said, however, that a very considerable portion of the blood allotted to the posterior part of the body, constantly leaves the fetal channels to be replenished in the placenta. Considered in a general way, it is

obvious that the circulation of the fetus greatly favors the head region, the proper growth of the nervous system being of much greater importance than that of the other tissues and organs.

The distinctive features of the fetal system may, therefore, be said to be the ductus venosus, the foramen ovale, the ductus arteriosus, the hypogastric arteries, and the umbilical artery and vein. The obliteration of these blood-vessels is initiated immediately after birth, but several days usually elapse before this process has been completed. Thus, the distal portions of the hypogastric arteries are usually found to be impervious at the end of the third or fourth day, while the obliteration of the ductus venosus and umbilical vein is not effected until the end of the first week and that of the ductus arteriosus not until the end of the third or fourth week.

CHAPTER XXIV

THE ARRANGEMENT OF THE MUSCULATURE OF THE HEART

THE VALVES OF THE HEART

The Structure of the Auricles and Ventricles.—The adult human heart measures about 125 mm. in length, 87 mm. in breadth, and 62 mm. in thickness. Its volume exhibits the following variations: 22 c.c. at birth, 155 c.c. during the fifteenth, 250 c.c. during the twentieth, and 280 c.c. during the fiftieth year. Thus, it will be seen that its growth is most rapid during early life. Beginning with about the fifteenth year, the heart of the male becomes larger than that of the female. At birth the organ weighs about 24 grams, at puberty 250 grams, and in adult life 310 grams. The heart of the adult female weighs about 255 grams. To begin with, the ventricles are equally heavy, but at the end of the second year the left weighs about twice as much as the right, this relationship of 2:1 being retained until death.

The wall of the heart is composed of three layers, namely a lining membrane, or *endocardium*, a median coat, or *myocardium*, and an outer investment, or *epicardium*. The outermost layer forms at the same time the inner or visceral half of the pericardium which is then reflected from the base of the heart to serve as the parietal half of this capsular investment. The space which is thus cut off from the general cavity of the thorax, is known as the pericardial sac. Its opposing surfaces are moistened with a few drops of a lymph-like fluid, called the pericardial fluid. The function of the latter is to lessen the friction which must necessarily be associated with the changes in the volume of the heart. The pericardium contains many elastic fibers which coalesce

with the adventitia of the large veins. Elastic fibers and a few smooth muscle cells are also scattered through the endocardium, and especially through the lining of the auricles. As far as the *function of the pericardium* is concerned, it may be stated that it exerts a restraining influence upon the musculature of the heart, insuring a certain compactness of its substance, and serving to counteract the effects of unusual degrees of pressure within its chambers. Thus, any defect in this enveloping membrane generally permits of a decided outward bulging of the cardiac substance which in turn may lead to an incompetency of the valves.

It is very suggestive that the heart of mammals is composed of a type of muscle tissue which occupies an intermediate position between the primitive smooth muscle and the specialized striated muscle. In fact, its high content in sarcoplasm would tend to ally it more closely with the former tissue. It is also of interest to note that in the lower forms the cardiac muscle is composed of actual cells possessing a spindle-like shape and an elongated nucleus. In these animals, the heart appears essentially as a simple tubular muscle, the different parts of which are intimately connected with one another by bridges of muscle tissue.

In the mammals, on the other hand, the mass of the ventricular musculature is completely separated from the auricles by a heavy deposit of connective tissue situated in the domain of the auriculo-ventricular groove. It is to be noted that the perimysium enveloping the muscle fibers increases very markedly at this level of the heart, while the muscle fibers decrease in number, their places being taken eventually by strong fibrotendinous rings, the so-called annuli fibrosi. These structures which occupy the auriculoventricular furrow, serve as the framework to which the different strands of muscle-tissue are fastened. But, while the auricles and ventricles of the mammalian heart are not united by direct bridges of muscle, they are brought into functional relation by a strand of musculonervous tissue which is known as the auriculoventricular bundle or the bundle of His.

In accordance with the low degree of pressure developed by the auricles, the musculature of these chambers appears as a thin capsule to which, however, a seemingly disproportionate strength is given by the *musculi pectinati*. These projecting strands of muscle tissue are especially numerous in the domain of the appendix auriculæ, where they encroach upon the main cavity in such a manner that saccular recesses are formed which are known as the foramina Thebesii. In this way, the capacity of the central expanse of the auricular cavity, which lies directly above the auriculoventricular orifice, may be greatly increased at any time without incurring the danger of over-distending and rupturing its wall. A circular depression upon the interauricular septum indicates the location of the *foramen ovale* of intra-uterine life. In addition, the right auricular cavity presents the orifice of the coronary sinus, guarded by the delicate valve of Thebesius. In the left

cavity, we observe the orifices of the pulmonary veins, generally four in number.

The musculature of the principal mass of the auricles is arranged as an outer *transverse* and an inner *longitudinal* layer.¹ Moreover, while each auricle really constitutes an anatomical and functional entity, a number of fibers of the superficial coat always pass from one side to the other, thus joining the two. In this way, a coördinated activity of the two chambers is assured. Circular fibers are much in evidence at the orifices of the larger veins and at the coronary sinus. It should be emphasized, however, that these muscular rings do not act as sphincters, but merely tend to lessen the size of the opening.

A more complicated relationship is presented by the musculature of the ventricles. As these parts are called upon to develop the force necessary to drive the blood through the distant vascular channels, it cannot surprise us to find that their walls possess a great massiveness and strength. Furthermore, as the left ventricle is destined to supply the blood-vessels of the greater circuit and thus to perform by far the greatest amount of work, it may be assumed that its wall is much thicker and stronger than that of the right cavity. In cross-section, the left cavity appears as a rounded orifice enveloped by a heavy frame of muscle-tissue, while the right compartment presents itself as a crescent-shaped slit limited externally as by a relatively thin layer of muscle (Fig. 130). It should be remembered, however, that the basal portion of the right cavity gradually assumes a more conical outline, and that the apex of the heart is formed exclusively by the left ventricle. Thus, if the heart is divided transversely beginning at its apex, the left ventricular cavity is opened first and the right cavity only after another section at a much higher level has been made.

Although the ventricular muscle fibers do not exhibit definite points of origin and insertion, it is permissible to assume that they begin in the fibrous tissue at the auriculoventricular junction; indeed, the entire ventricular network may be likened to a muscular basket fastened above to the annuli fibrosi. Three distinct layers are discernible, namely, an outer, a middle, and an inner. The fibers of the *outer* and *inner* layers are arranged longitudinally, while those of the median coat are directed transversely to the long axis of the heart and pass, therefore, circularly around the lumen of the ventricular cavity. Beginning at the base of the heart, the outer fibers extend spirally toward the apex, but in such a way that their general

FIG. 130.—TRANSVERSE SECTION THROUGH HEART OF DOG, 3 CM. ABOVE APEX TO SHOW SHAPE AND POSITION OF VENTRICULAR CAVITIES.

¹ Krehl, Abhandl. der sächs. Gesellsch. der Wissenschaften, xvii, 1891, 346.

direction is oblique. Rather numerous on the left side, they form merely a thin superficial layer in the right ventricle. At the apex they again curve upward and are finally inserted in the septum and adjoining papillary muscles. The inner fibers begin in the apical whorl and extend almost in a straight line toward the base, but it is not quite correct to look upon them merely as continuations of the outer fibers.

Mall¹ divides the superficial fibers into the bulbospiral and sinospiral. The former begin at the conus, the left side of the aorta and

FIG. 131.—SCHEMA TO SHOW THE COURSE OF THE SUPERFICIAL AND DEEP FIBERS OF THE BULBOSPIRAL AND SINOSPIRAL SYSTEMS. THE HEART IS VIEWED FROM THE DORSAL SIDE.

BS, superficial bulbospiral system; *BS'*, deep bulbospiral system; *SS*, superficial sinospiral system; *SS'*, deep sinospiral system; *C*, circular fibers round the conus; *C'*, circular fibers round the base of the aorta and the left ostium; *LRV*, longitudinal bundle of right ventricle, from membranous septum to right ventricle; *IV*, interventricular or interpapillary layer. (*Mall.*)

the left side of the left ostium venosum and pursue a spiral course to the apex, where they enter into the formation of the posterior horn of the vortex. Some of these fibers end in the septum and some in the posterior wall of the left ventricle where they terminate in the basal portion of this papillary muscle. The fibers of the sinospiral system originate from the posterior aspect of the heart in the vicinity of the right venous ostium. They pursue a spiral course to the apex, where they form the anterior horn of the vortex and terminate in the anterior wall of the left ventricle and corresponding papillary muscle. In addition, Mall recognizes a deep bulbospiral and sinospiral system

¹ *Am. Jour. of Anatomy*, ii, 1911, 211.

of fibers. Both are directed more transversely than the superficial layers. The former encircle the left cavity and the latter the right cavity, and finally surround the large blood-vessels at the base of the heart.

These two longitudinal layers, form, so to speak, a sling-like support for the *circular fibers* which are especially numerous on the left side, and give an unusual volume and strength to this compartment. It must be evident that the circular coat is the most important dynamic factor, because its constrictor action serves to lessen the lumen of the ventricular cavity in a most decided manner, thus giving rise to the pressure which is required to drive the blood through the system. It should be emphasized, however, that although each ventricle is constructed in such a way that it forms a muscular unit, the joint action of the two is assured by certain strands of fibers which pass from side to side and envelop both compartments.

On contraction, each ventricular mass of tissue assumes a rounded outline so that the two compartments become sharply differentiated from one another by a groove which extends obliquely downward from a point above and on the right side to a point below and on the left. Moreover, in accordance with the general direction of the fibers of the outer coat, the entire ventricular mass is turned at this time slightly around its longitudinal axis so that the apical center is rotated from left to right and forward. For this reason, a more extensive area of the left side of the heart is brought into view during this period; and naturally, only the left ventricle then presents itself below the interventricular groove, because the apex is formed solely by the musculature belonging to this compartment.

The Arrangement of the Valves.—With the exception of the appendix auriculæ, the cavity of the auricle presents a perfectly smooth internal surface. In the ventricles, on the other hand, open spaces are encountered solely below the orifices of the aorta and pulmonary artery. The former is designated as a rule as the aortic vestibule and the latter as the conus arteriosus. The remaining space of each ventricle is rendered rugose and uneven by numerous projecting bundles of muscle-tissue which appear in the shape of (a) columns raised in relief from the wall, (b) as isolated cords of tissue stretching directly through the cavity, and (c) as free conical and nipple-shaped elevations projecting for a short distance into the lumen of the cavity. The first are known as *columnæ carneæ*. Their function seems to coincide with that of the general mass of the cardiac tissue. The second, called *moderator bands*, are found most frequently in the right cavity. They arise as a rule from the interventricular septum and are inserted in the outer wall. Obviously, their purpose is to prevent an excessive outward movement of the latter and an undue distention of the cavity as a whole. The third, commonly referred to as the *papillary muscles*, are in functional relation with the principal mass of the cardiac musculature and serve as points of attachment for the *chordæ tendineæ*,

which, as the name indicates, are tendinous cords extending from here to the overlying valve flaps.

The Auriculoventricular Valves.—It has been stated above that the blood flows through the heart in a perfectly definite direction, because the contraction of the ventricles does not take place until the contraction of the auricles has been completed, and because the orifices connecting the different chambers of this organ are opened and closed in perfect harmony with the activity of the cardiac muscle. There are really two ways in which the cardiac orifices could be closed: namely, by heavy rings of muscle tissue which by their sphincter-like action obliterate the passage in the manner of the diaphragm of a photographic camera, or by membranous flaps which, in the manner of a door, swing directly across the openings. Clearly, the closure of an orifice by a layer of circular musculature is an action which requires power and, therefore, necessitates the expenditure of a considerable amount of energy. If this mechanism were actually in use in our heart, it would mean that the pressure developed by this organ would have to be apportioned in part to the closure of its orifices, and in part to the blood as driving force. For this reason, the use of valves must be considered as a much more economical means, inasmuch as it does not necessitate a division of the cardiac energy. The different valve flaps are moved into place passively by the relative degrees of pressure upon their two surfaces, and hence, all the power developed by the heart may be directed to the single purpose of propelling the blood. In this way, the closure of the valves is accomplished, so to speak, incidentally in the course of the general muscular contraction.

The auriculoventricular openings are large and are especially adapted for a quick transfer of blood. The left is oval in shape and smaller than the right which possesses a rounded triangular outline. Both orifices are surrounded by fibrous rings which are connected with the mass of the fibrocartilaginous tissue situated at the auriculoventricular junction. The different valve flaps are composed of double folds of endocardium, strengthened by fibrous tissue and containing a few elastic fibers and muscle cells. The latter are arranged radially and are connected with the auricular musculature. The basal portions of the flaps are fastened to the walls of the orifice, while their tips and thin margins are free and project far into the cavity.

The left valve, known as the mitral, is composed of two triangular flaps of unequal size, while the right, or tricuspid, consists of three flaps. Both valves yield solely in a downward direction and on closure assume a position transversely across the opening. A perfect approximation of the different flaps is made possible, on the one hand, by the muscle tissue forming the wall of the orifice, and, on the other, by the chordæ tendineæ with which their lower surfaces are connected. Obviously, the contraction of the former gives a certain firmness to the frame in which the valve flaps are hung so that their basal portions become fixed, while their tips attain a wide range of movement. In

addition, this firmness and greater prominence of the wall of the orifice must tend to lessen the size of the passage. The arrangement of the *chordæ tendineæ* must seem very perplexing to the casual observer. On closer examination, however, it will be seen that they arise from the papillary muscles which are situated at some distance below the basal portions of the different valve flaps. A very clear picture of the course pursued by them may be obtained in the left ventricle, in which only two papillary prominences are present. In the right cavity,

on the other hand, the conditions are less simple, because we find here three papillary projections and, in addition, also a number of *chordæ* which origi-

FIG. 132.

FIG. 132.—HEART OF THE COW, WITH LEFT AURICLE AND VENTRICLE LAID OPEN. (Müller.)

a, Root of the aorta; b, spaces in the wall of the auricle; c, c, orifices of the pulmonary veins; l, l, pulmonary veins; p, p, papillary muscles; q, q, columnæ carneæ. A, orifice of the aorta; K, left ventricle; S, septum; V, left auricle; W, lateral wall of left ventricle; 1, 1, 2, leaflets of mitral valve.

FIG. 133.

FIG. 133.—SCHEMA TO SHOW FAN-LIKE DISTRIBUTION OF CHORDÆ TENDINEÆ (C) FROM A SINGLE PAPILLARY MUSCLE (P), SITUATED UNDERNEATH (V), TWO ADJOINING VALVE FLAPS.

nate from the septum itself. Very soon after they leave their places of origin, the individual *chordæ* divide into smaller strings which extend fan-like through the cavity to be inserted eventually upon the free margins and more centrally located areas of the flaps above them. Moreover, as the papillary muscles are placed as a rule almost vertically below the points of union between two neighboring flaps, each colony of *chordæ* concerns itself chiefly with the two margins nearest to them. In reaching their points of insertion they frequently cross one another, but without impairing their movement.

The structure and general arrangement of the *chordæ* prove very

convincingly that they are instrumental in approximating the different valve flaps. Thus, by permitting the different flaps to be moved into a position transversely across the orifices and no farther, they serve a purpose very similar to that of the guy-ropes of a sail. Secondly, as a number of chordæ are always inserted upon the central area or body of the flaps, they prevent the bulging or bellying of the entire valve into the auricular cavity. Thirdly, as the papillary projections from which the chordæ arise are usually placed vertically below the space between two adjoining flaps, and as the individual strings are inserted upon the margins of both, they must necessarily exert a traction toward a common center which is situated midway below the planes of the two flaps. In this way the margins of the different flaps are pulled together transversely and are then held firmly in place. It may be assumed that the papillary muscles take part in the general contraction of the ventricles, thereby furnishing a more solid basis for the chordæ to act upon; in fact, it may be said that the contraction of these projections exerts a certain traction upon them which facilitates their unfolding and the approximation of the valve-flaps.

The auriculoventricular valves are opened very soon after the cessation of the contraction of the ventricles. Gradually, as the blood flows into the auricles from the central veins, the intra-auricular pressure is raised above that prevailing in the now passive ventricles. In consequence of the higher pressure exerted upon their upper surfaces, the flaps are forced slightly apart with the result that the blood now rushes into the ventricular cavity. It should be remembered, however, that the flaps are not moved as a door would be on opening it, because their basal portions are attached to a rather rigid cushion of tissue and remain, therefore, relatively fixed. Their tips, on the other hand, are bent sharply downward so that each flap assumes the shape of a crescent, the concavity of which faces the ventricle.

The auricular contraction following very shortly after the initial opening of the auriculoventricular valve, renders the orifice between these chambers more funnel-shaped. The blood being driven directly into the narrowest part of this passage opposite the tilted tips of the flaps, is thus directed into the central expanse of the ventricles without being able to form secondary currents or whorls which might seriously impair its flow. Quite naturally, when this column of blood traverses the ostium, the flaps are pushed far apart, but are not brought into actual contact with the ventricular wall. The space between them and the surface of the latter is filled with blood. This is of great dynamical importance, because if the flaps were forced against the wall, it would be difficult to dislodge them and to move them into the position of closure. Obviously, the latter movement can only be effected if their under surfaces remain exposed to the ventricular pressure.

The contraction of the auricles fills the ventricles to their utmost capacity so that their walls become fully distended and remain so until the end of the auricular contraction. Directly thereafter,

however, the ventricular wall recoils and exerts a static pressure upon the blood with which this cavity is now filled. Secondary currents are set up which strike the surfaces of the valve flaps and push them upward in the direction of their position of closure. This static back pressure, however, is not the only factor upon which the approximation of the valve flaps depends; in fact, it merely serves the purpose of "floating" them into their initial position of closure, while the actual snapping together of their marginal areas is accomplished by the suction which must necessarily result in the wake of the column of auricular blood as it clears the auriculoventricular orifice.¹ When the contraction of the auricles ceases, the driving force is suddenly withdrawn. The column of blood, however, rushes on, with the result that an area of negative pressure is developed in the rear of it which immediately draws the flaps almost transversely across the center of the orifice. Thus, it will be seen that the final closure of the valves is accomplished by the "breaking" of the column of auricular blood and clearly, as the flaps swing in from the side, the blood is cut off very sharply so that a backward movement of it is impossible under ordinary conditions.

The Semilunar Valves.—The conditions met with at the aortic and pulmonary orifices, are quite different from those encountered at the auriculoventricular openings. In accordance with the high degree of pressure developed by the ventricles, their exits are narrow and surrounded by solid walls. Each orifice is guarded by three separate segments which are fastened end to end against the internal surface of these blood-vessels. Each segment exhibits a cup-like shape, its convex surface being directed toward the heart. The basal portions of the flaps rest upon a solid cushion of the ventricular substance, while their free ends project far into the lumen of the blood-vessel. No special structures are present to hold them in place.

When the ventricles contract and drive the blood through these slit-like orifices into the arteries, the tips of the different valve-flaps are pushed far apart, but it should be emphasized that they are not forced into contact with the wall of the blood-vessel.² Such a result is practically impossible, because the basal portions of the flaps are well protected against the ventricular stream by the heavy cushion of muscle tissue to which they are fastened, and because the beginning segment of each blood-vessel is very much larger than its more periph-

FIG. 134.—LONGITUDINAL SECTION THROUGH THE ROOT OF THE AORTA TO SHOW CUP-LIKE SHAPE OF SEMILUNAR VALVE FLAPS.

¹ Henderson, *Am. Jour. of Physiol.*, xvi, 1906, 325; also see: Henderson and Johnson, *Heart*, iv, 1912, 69.

² Ceradini, *Der Mechanismus der halbmondf. Klappen*, Leipzig, 1872.

eral segment. The latter peculiarity is dependent upon the fact that the wall opposite each valvular segment is distended to form a pocket, the so-called sinus of Valsalva.¹ A certain quantity of residual blood is always retained in these enlargements. From the right and left fossæ arise the two coronary arteries which supply the substance of the heart.

The semilunar valves are closed directly after the completion of the contraction of the ventricles. The mechanism involved in this process is similar to that described previously. As the basal portions

FIG. 135.—DIAGRAM TO SHOW POSITION OF SEMILUNAR VALVE FLAPS ON CLOSURE.

I, longitudinal section; II, transverse section; V, ventricle; A, aorta; FV, fossa of Valsalva; C, corpora arantii.

of the different segments are relatively fixed, their free tips are snapped together by the "breaking" of the ventricular jet of blood. The flaps are then held firmly together by the pressure existing in the arteries. As is indicated in Fig. 135, this force is directed not only in a straight line against their outer surfaces, but also transversely against their marginal zones. In this way, the under surfaces of their tips are forced firmly against one another so that a displacement and inversion of the segments is quite impossible. Moreover, it is of interest to note that the marginal

area of the tip of each flap gives lodgment to a fibrous thickening which rises above the general surface and is adjusted in such a way that it closely fits into the neighboring nodules. In this way, even the most central regions of these arterial orifices are made perfectly secure when the valves are closed. These granular bodies are known as the corpora Arantii.²

CHAPTER XXV

THE CARDIAC CYCLE (REVOLUTIO CORDIS)

The Number of Cardiac Cycles.—The blood reaches the venous vestibule of the heart under a very low pressure and leaves its arterial orifices under a relatively high pressure. This fact shows that this organ acts as a pump. It develops one of the fundamental attributes of the circulation, namely, the pressure necessary to drive the blood

¹ Named after the Italian anatomist Valsalva of Bologna, born in 1666.

² Named after Julius Caesar Aranzi of Bologna, an Italian anatomist, born in 1530.

through the system. Its action, however, is not comparable to that of a piston-pump, but rather to that of a rubber bulb when compressed by the hand. The contraction of its muscular substance diminishes the size of its cavities so that the blood contained therein is subjected temporarily to a high degree of pressure. Each contraction of the heart, or systole, is immediately followed by a period of relaxation, or diastole, and the latter in turn by a period of rest. These three phases together constitute the cardiac cycle.

The general rule, that the frequency of the heart is indirectly proportional to the size of the body, finds its application throughout the animal kingdom, but particularly among the warm-blooded animals. This fact is clearly brought out by the following compilation:

Elephant.....	25 cycles in a minute
Camel.....	30 cycles in a minute
Lion, horse, ox.....	40 cycles in a minute
Donkey.....	50 cycles in a minute
Panther.....	60 cycles in a minute
Sheep.....	70 cycles in a minute
Man.....	70 cycles in a minute
Dog.....	100 cycles in a minute
Rabbit.....	150 cycles in a minute
Mouse.....	175 cycles in a minute

Among the cold-blooded animals this relationship is not always apparent, because their bodily functions are more markedly influenced by outside conditions. The heart of the frog or turtle beats 40 to 50 times in a minute, a rather slight frequency for such small animals. The fact that the cardiac frequency is greater in small animals, need not surprise, because their metabolism is greater on the whole than that of larger animals. This must necessarily be so, because as the former present a proportionately larger surface to the medium in comparison with their mass, they must lose larger amounts of heat. This greater loss is counteracted by more intense metabolic changes.

The human heart is subject to various influences, such as age, sex, temperature, barometric pressure, posture, muscular movements, emotions, etc. Before birth, the heart of the female beats about 140 to 145 times in a minute, and that of the male about 130 to 135 per minute. Conditions being favorable, it is possible to make use of this fact in foretelling the sex of the fetus. It is still very frequent at birth, but its rate is markedly decreased during the first year of extra-uterine life and more gradually during the subsequent years. Late in life its frequency is again increased.

At birth.....	140
Infancy.....	120
Childhood.....	100
Youth.....	90
Adult age.....	75
Old age.....	70
Extreme old age.....	75-80

On account of the larger size of the male body, the heart of the male is less frequent than that of the female, but if a comparison is made between men and women of equal size, no significant differences will be found. The figures ordinarily given for man are: 70 beats in the male, 80 in the female, and 90 in children. Even very slight muscular movements increase the rate, while rest decreases it, the lowest value being found after continued quietude in the horizontal position. On assuming the erect position the heart beats somewhat faster. The figures frequently given are: 75 on lying down, 77 on sitting up, and 85 on standing erect. Its frequency is also augmented by warm food, or by increasing the temperature of the surrounding medium. The same result is obtained if the temperature of the body, as a whole, is raised, as in fever. This augmentation may be shown very clearly by perfusing the heart of a cold-blooded animal with Ringer's solution which it is possible to heat gradually. The force and rate of the heart beat then increase with the temperature until a maximum has been reached at about 30° C. Beyond this point the beats become slower and assume an irregular and fibrillar character until they stop entirely. Very similar tests have been made by N. Martin upon the heart of the cat. This organ ceases to beat at about 17° C. and also if the temperature of the perfusing liquid is raised to 44° or 45° C. The acceleration obtained during fever may, therefore, be due in large part to the direct action of the blood as it traverses the cardiac chambers. Most generally, the heart of warm-blooded animals beats more quickly and more strongly during the cold seasons of the year, which change is in agreement with the fact that their metabolic activity is greater in winter than in summer. The reduced metabolism and heat production coincident with low degrees of temperature must be held responsible for the decided decrease in the frequency of the heart of hibernating animals. In the bat, for example, a frequency of 28 in a minute during this period gives way to 200 per minute during the summer months. Muscular exercise increases the frequency of the heart, because the tissues then undergo more intense metabolic changes and require a more copious supply of blood. Decreases in the oxygen content or increases in the carbon dioxide content of the blood increase the rate.

The Character of the Contraction.—Attention has already been called to the fact that the different segments of the heart do not contract simultaneously, but successively, the musculature nearest the venous vestibule being activated first and that nearest the apex last of all. Thus, the contraction of this organ presents several of the characteristics of a peristaltic wave, progressing from its base to its apex. For this reason, it has been said to be similar in character to the curve recorded by skeletal muscle when stimulated with a tetanic current. This fact proves that the cardiac musculature remains in the state of systole for some moments before it again relaxes. Clearly, this peculiarity in the manner of its contraction must tend to produce a

thorough emptying of the different chambers of the heart. But, as it has been shown that single narrow segments of cardiac muscle give typical twitch-like contractions, it must be concluded that the tetanic character of the systolic movement of the entire organ can only be due to the fact that its different segments contract successively in the direction from base to apex.¹

The Speed of the Contraction Wave.—The progressive character of the contraction of the heart may be studied best in the lower forms in which the systole of the sinus antecedes that of the auricle, and the systole of the latter that of the ventricle. In a similar way it may be observed in the mammalian heart that the auricular contraction is separated from the ventricular by a definite interval which becomes especially noticeable in an organ shortly before it ceases to beat. A graphic record of the contraction wave may be made by placing long writing levers upon the basal and apical portions of an exposed heart. If these levers are permitted to write in the same vertical line and in relation with a chronograph registering the time in seconds, it is a simple matter to compute its speed, because the distance between the levers can be measured directly with a ruler. In this way, it has been found by Reid and Waller² that the velocity of this wave is 10 cm. in a second in the heart of the frog and 80 cm. per second in that of the sheep. Bayliss and Starling³ give the value of 300 cm. in a second for the dog's heart. In accordance with these figures, it must be concluded that the wave consumes at least 0.05 sec. in its passage across the human heart. In fact, upon the basis of electrical measurements made by Kraus and Nicolai,⁴ an even longer time seems to be required, namely about 0.2 sec., before the distalmost segments of the ventricles become involved.

The Path of the Contraction Wave.—In the mammalian heart, the musculature of the ventricles is completely separated from that of the auricles by a zone of fibrous tissue.⁵ At one point, however, the two masses are connected by a strand of modified muscle tissue which is known as the bundle of His⁶ or the auriculoventricular bundle. This bridge begins in the basal portion of the interauricular septum, directly above the septum fibrosum atrioventriculare. It arises in a complex nodular accumulation of cells and fibers which is usually re-

¹ Walther, Pflüger's Archiv, lxxviii, 1900, 597.

² Phila. transactions, 198, 1888, 230.

³ Proc. Royal Soc., 1892, 211.

⁴ Berliner Klin. Wochenschr., 1907, Nr. 25 and 27.

⁵ It has been known for some time that muscular connections between the auricles and ventricles are present in the fish, reptiles and amphibians. The existence of similar connections in mammals has been denied until 1893, when G. Paladino and Stanley Kent put forth the claim that a path of this kind exists. Their observations, however, cannot be regarded as valid, because their descriptions are very indefinite, while the illustrations, showing certain connections between the left auricle and ventricle, apparently do not picture the conditions as they actually are.

⁶ Named after W. His, Jr. (1893), Professor of Anatomy at Leipzig (1863).

ferred to as the auriculoventricular node. Having pierced the fibrous tissue of the groove, it passes along the interventricular septum immediately below the endocardium, and divides eventually into two branches. This bifurcation takes place at about the point where the posterior and median flaps of the aortic valve are joined. The main bundle of the average human heart is about 18 mm. in length and 1.5 to 2.5 mm. in width. One of its branches is distributed to the right, and the other to the left ventricle, but before the distant musculature is reached, the bundle spreads out fan-like and forms an intricate network of fibers. This peripheral ramification was clearly recognized by Purkinje, but no particular attention was paid to it until Tawara¹ proved that its constituents are intimately connected with the bundle of His.

FIG. 136.—LEFT VENTRICLE LAID OPEN TO DISPLAY THE INTERVENTRICULAR SEPTUM. THE COURSE OF THE AURICULOVENTRICULAR BUNDLE AND ITS RAMIFICATIONS ARE SHOWN IN BLACK. (After Tawara.)

It has previously been stated that in the lower animals the contraction wave originates in the sinus venosus, and eventually reaches the apex of the ventricle by travelling across bridges of muscle tissue. The sinus, therefore, must give lodgment to a certain group of cells in which the wave of excitation is generated. For this reason, this particular area of the sinus has been designated as the pacemaker of the heart.

Very similar conditions are met with in the mammals. Thus, the embryonic heart presents the sinus venosus as a separate cavity which is bounded by the orifices of the venæ cavæ, the Eustachian valve and the interauricular septum. The adult organ, on the other hand, does not possess a distinct vestibular enlargement, because the sinus has been incorporated in the main cavity of the auricle. The remnants of the Eustachian and venous valves, however, are still discernible in conjunction with the tænia terminalis. Even a very casual observa-

¹ Pflüger's Archiv, cii, 1906, 300.

tion of the beating mammalian heart must show that the contractions begin in the tissue situated at the junction of the superior vena cava with the right auricle. This region which corresponds to the sinus reuniens of the embryonic organ, constitutes the pacemaker of the higher type of hearts. One of these veno-auricular accumulations of tissue has been adequately described by Wenkelbach. In confirmation of this work, Flack and Keith¹ have applied to this area the name of sino-auricular node, the further assertion being made by these investigators that it is intimately connected with the bundle of His.

It must be concluded, therefore, that the stimulus to contract arises in the specialized tissue forming the sino-auricular node. When

FIG. 137.—THE AURICULOVENTRICULAR BUNDLE AND ITS TERMINAL RAMIFICATIONS IN THE INTERIOR OF THE VENTRICLES (FROM MODEL CONSTRUCTED BY MISS DE WITT ON BASIS OF DISSECTIONS).

The division of the bundle into right and left branches is shown, and the ramifications of each of these branches in the interior of the right and left ventricles. The branching system in the left ventricle is incomplete in the model, as the outer wall of this ventricle had been removed in the dissection. (*Howell.*)

this area is warmed or cooled, the frequency of the heart as a whole is either increased or decreased; and this effect cannot be produced if other regions of this organ are subjected to changes in temperature.² Furthermore, it has been found by Gaskell³ that the rhythmic power of the muscle tissue of the venous vestibule is greater than that of the ventricular musculature.

The wave of excitation is propagated from the sino-auricular node to the different segments of the auricles as well as to the auriculoventricular node. Although the statement is generally made that the

¹ Jour. of Anat. and Physiol., xli, 1906, 172, and M. Flack, Jour. of Physiol., xli, 1910, 64.

² Erlanger and Blackman, Am. Jour. of Physiol., xix, 1907, 125; also see: Schlomovitz and Chase, Am. Jour. of Physiol., xli, 1916, 112.

³ Schäfer's Textbook of Physiol., 1900.

auricles contract together, accurate measurements have shown that the left one lags somewhat behind the right. The interval, of course, is extremely brief; it amounts to only 0.01 to 0.03 sec. The excitation wave finally reaches the papillary bases of the ventricles by way of the bundle of His and its distal ramifications. The wave itself is accurately timed so that a perfect coördination between the different segments of the heart is assured. We have previously noted that a period of almost 0.2 sec. elapses before the wave arrives in the distalmost muscle strands of the ventricle, but naturally, the conduction is not equally rapid in all parts of the heart. Thus, it has been found that the bundle of His conducts rather slowly, because the wave attains here a velocity of only 10 to 15 cm. in a second. This fact is of interest, because, as has previously been shown, the ventricle contracts after the auricle, the interval between their systoles amounting to 0.12–0.2 sec. Hence, the resistance in this bridge of tissue has been adjusted in such a way that a perfect sequence of contraction is obtained.

Two views are held regarding the manner in which the ventricular musculature is activated. It was formerly believed that the segments situated nearest the auriculoventricular groove, contract first, while those closest to the apex are involved last. The results of electrical measurements and of cinematographic records of the beating heart, taken by Nicolai and others,¹ however, have shown that the excitation wave is conducted directly to the papillary projections, and hence, it must be concluded that this particular system of the ventricles is activated first. The contraction wave spreads from here to the oblique and circular muscle fibers. Clearly, this view is entirely in accord with the anatomical arrangement of the conducting path, because, as has been stated above, the main bundle of His is enveloped in a sheath of fibrous tissue, while its terminals, the fibers of Purkinje, are directly traceable to the papillary muscles.

Heart-block.—The preceding statements find amplification in the observations of Gaskell,² showing that the passage of the wave of excitation through the hearts of frogs and turtles may be greatly retarded by compressing the tissue forming the auriculoventricular groove. While this end may be attained with the help of a pair of forceps, a better way is to adjust a screw-clamp to this region, which enables the experimenter to grade the pressure more accurately and to obtain different degrees of blocking. Under ordinary conditions every contraction of the auricles is followed by a contraction of the ventricles, because the wave of excitation meets with no obstacle in its passage through the bundle. If the latter is now thoroughly compressed by the closure of the clamp, the impulse is blocked at the seat of the injury and cannot reach the ventricles. This particular segment of the heart now ceases to beat, while the auricular portion continues its activity as previously estab-

¹ Braun (*Herzbewegung und Herzstoss*, Fisher, Jena, 1898), and Rehfish (*Berliner klin. Wochenschr.*, 1908, Nr. 26).

² *Jour. of Physiol.*, iv, 1883, 66.

lished. Eventually, however, the ventricle develops a rhythm of its own which is made possible by its inherent power of contraction. This condition constitutes total heart-block. It must be remembered, however, that there are also certain intermediate stages of this affection which arise whenever the obstruction is not complete. This enables the wave of excitation to break through at intervals. Thus, it may come to pass that only every second, or every third or fourth auricular systole is able to elicit a regular ventricular contraction, thus establishing a 2:1, 3:1, or 4:1 rhythm. In other words, while one single wave may not be sufficiently powerful to overcome the resistance placed in the path of conduction, the sum total of two or three or more may suffice to break through this obstruction. And naturally, whenever the ventricle is thus made to respond to an auricular beat, the resulting systole must exhibit the characteristics of a normal contraction, because under ordinary conditions, the activity of cardiac muscle does not vary with the strength of the stimulus, but remains constant.

It has been stated by Kent¹ that these observations, although originally made upon the heart of the frog, may be duplicated in mammals, but the evidence submitted in support of this statement cannot be regarded as at all convincing. In conformity with the work of Woolbridge and Tigerstedt,² it has been found by His that the auricles and ventricles may be functionally dissociated not only by destroying the interauricular septum, but also by causing a local injury to the auriculoventricular bundle. These results have been confirmed and much extended by Erlanger.³ In man, heart-block commonly arises in consequence of endocardial lesions or tumors involving the origin and main strand in the bundle of His. It may also be caused by a general diminution in the irritability of the ventricular musculature, a condition which may result in the course of syphilis and septic infections and intoxications.

Fibrillation of the Cardiac Muscle (Delirium Cordis).—When in fibrillation, the musculature does not respond with strong and unified contractions, but with a continuous wavy and oscillatory motion. This condition may be more or less localized or may affect the organ as a whole. When restricted to the auricles, as it frequently is, it is designated as auricular fibrillation, and when involving the ventricles, as ventricular fibrillation. It follows strong electrical, thermal, or mechanical stimulation of the cardiac muscle as well as obstructions to the coronary circulation. It is scarcely possible to relieve this condition after it has been firmly established. In this regard, it differs from the so-called flutter which signifies an extreme increase in frequency, sometimes to 300 or 400 in a minute without marked alteration in the character of the individual beats.

¹ Jour. of Physiol., xiv, 1893, 233.

² Archiv für Physiol., 1883 and 1884.

³ Am. Jour. of Physiol., xvi, 1906, 160; and xxx, 1912, 395.

The cause of this sudden loss of regularity of contraction is not fully understood. Kronecker¹ believes that it is due to the destruction of the coördinating cardiac center, while McWilliam² states that it is dependent upon an interference with conduction. The work of Garrey³ has greatly strengthened the block-hypothesis of Porter⁴ which proposes that the fibrillation is due to an interruption of the contraction wave. In consequence of this blocking, this wave is prevented from running its usual course until the normal coördinated action of the cardiac musculature gives way to the confused "circus" motions of fibrillation. A similar confusion of contraction may be produced in the tongue by reestablishing the circulation after it has been interrupted for some time. As this organ embraces muscle fibers which are arranged in different directions, it has been thought that this peculiar motion is caused by a loss of functional continuity between the adjoining areas of tissue. It is possible that a similar dissociation takes place in the fibrillating heart.

A fibrillating heart, or ventricle, is, of course, quite unable to expel the blood and to sustain the circulation. Death results very suddenly. A fibrillating auricle, on the other hand, is not necessarily incompatible with life, because the ventricles are still in a condition of responding. To be sure, the contractions of the latter become irregular, because they are now played upon by numerous impulses derived from the fibrillating auricles. This condition is characterized by an irregular arterial pulse and an absence of the auricular summit from the venous pulse, as recorded from the external jugular vein. The electrocardiogram taken at this time does not show the P-wave which represents the electrical variation produced by the normally acting auricles.

CHAPTER XXVI

THE PHENOMENA NOTED DURING EACH CARDIAC CYCLE

The different cardiac cycles follow one another in rapid succession, every additional one adding another unit of work to that already accomplished. Like any other mass of living substance, cardiac muscle generates mechanical, thermal, and electrical energy. The first of these is at present of greatest interest to us, because it furnishes the basis for the dynamics of the circulation. While the heart is engaged in this process of kinetically innervating the blood, it exhibits

¹ Compt. rend., Soc. de Biol., 1891.

² Jour. of Physiol., viii, 1887.

³ Am. Jour. of Physiol., xxi, 1908, 283.

⁴ Ibid., vi, 1902, 25.

a number of phenomena which may be conveniently dealt with under the following headings: (a) the changes in its form, (b) the generation of electrical energy, (c) the production of sounds, (d) the variations in pressure within its chambers, and (e) the changes in the position of its valves.

A. THE CHANGES IN THE FORM OF THE HEART

Methods of Registration.—The procedures most frequently employed for determining the changes which the heart undergoes during its systolic and diastolic phases, may be arranged in the following manner:

(a) Observation with the help of linear measuring instruments. (Ludwig, 1843.)

(b) Graphic registration by means of ordinary writing levers which are placed horizontally upon different parts of the heart (von Frey), or with the help of suspended levers which are connected with the cardiac musculature by strings. (Gaskell, 1882, and Engelmann, 1892.)

(c) Photographic, cinematographic, and radiographic registration. Orthodiagraph. (Zuntz and Schumberg, 1896, Buchard, 1898, and Braun, 1898.)

(d) Acupuncture, the insertion of long needles into different regions of the heart while the chest remains closed. (Jung, 1836, and Hayercroft, 1890.)

Nearly all investigations of this kind have been made either upon the excised heart or upon the heart while freely exposed to the view

FIG. 138.—DIAGRAM TO SHOW HOW THE BEATING FROG'S HEART ADAPTS ITSELF TO THE SURFACE UPON WHICH IT RESTS. THE DOTTED LINE INDICATES DIASTOLE.

by removing the ventral wall of the thorax. Quite obviously, either one of these procedures cannot be regarded as perfect, because it places this organ under abnormal conditions and tends, therefore, to disturb its normal activity. At the present time, however, this difficulty cannot be avoided and hence, it becomes necessary to correct any errors from this source by indirect evidence. Inasmuch as the consistency of the cardiac substance is soft during diastole and firm during systole, the organ as a whole must necessarily adapt itself to its surroundings and undergo certain changes in its form which, so to speak, are forced upon it. Even the normal heart *in situ* is not fully protected against the different degrees of traction which are brought to bear upon it whenever the body as a whole is made to assume an unusual position.

In endeavoring to obtain a composite picture of the changes in the form of the beating heart, attention should first be called to the altera-

tions in its shape, and secondly, to the alterations in its position. Concerning the former, the general statement may be made that its longitudinal and transverse diameters are decreased during systole, while its anteroposterior diameter is increased. In this way, the base and apex of the organ are brought closer together, while the outline of its basal portion is changed from an ellipse to a circle. For this reason, a diastolic heart always appears to be thicker along its borders than near its center, while the organ as a whole more nearly conforms to the general outline of the surface upon which it is resting. It is also evident that the systolic heart executes a rotatory movement which under ordinary conditions of experimentation remains more closely confined to its apical portion. In accordance with our previous

FIG. 139.—SHOWING LOCATION OF APEX BEAT.

The position of the aortic semilunar (+) and mitral (Δ) valves are indicated in red and that of the pulmonary semilunar (+) and tricuspid (Δ) in blue.

observation that the superficial fibers of the ventricle pursue in general an S-shaped course and form a whorl at the apex, it may be inferred that the rotation takes place from left to right.

The Cardiac Impulse (Impulsus Cordis).—On observing the external surface of the chest in the region of the apex of the heart, it is noticed that the thoracic wall is made to bulge outward with every systolic movement. In men, the greatest prominence is attained in the fifth intercostal space slightly to the right of the left mammillary line, which represents the perpendicular drawn through the left nipple. In woman, this impulse is more frequently observed in the

fourth intercostal space and is not so clearly betrayed on account of the interposition of a layer of mammary tissue. The area so affected measures about 2 cm. in diameter.

In accordance with the statements just made, it is possible to assign three causes to this impulse, namely: (a) the change in the outline of the basal portion of the heart, (b) the elevation or erection of the ventricle, and (c) the spiral rotation of the apex from left to right and from behind forward. We have seen that the cross-section of the base of the diastolic heart is elliptical while that of the systolic organ is circular. This change, as is clearly portrayed in the accompanying schema (Fig. 140), tends to decrease the distance between the wall of the thorax and the anterior surface of the heart. The base

FIG. 140.—TRANSVERSE SECTION THROUGH THE CHEST TO SHOW THE CHANGES IN THE SHAPE OF THE BASE OF THE HEART ON SYSTOLE.

The systolic heart (dotted line) lies closer to the chest wall.

FIG. 141.—LONGITUDINAL SECTION THROUGH THE CHEST TO SHOW THE FORWARD AND UPWARD MOVEMENT OF THE APEX DURING THE SYSTOLE (DOTTED LINE) OF THE VENTRICLES.

of the organ is thus moved nearer the chest wall. It should also be remembered that, in man, the space intervening between the heart and the wall of the thorax, is filled by the marginal area of the left lung. As this organ is more fully distended during inspiration, its border is forced farther forward in the direction of the median line, while during the subsequent expiration it again recedes laterally. It may be inferred, therefore, that the layer of pulmonary tissue interposed between the heart and the thoracic wall, is thinner during expiration than during inspiration and that the organ as a whole approaches the thoracic wall more closely during the former period. For this reason, the cardiac impulse, or apex beat, is more conspicuous during expiration. In the second place, it need scarcely be emphasized that the ventricle is more flaccid when relaxed than when contracted, so that its apex must assume a more dependent position during the former period. The contraction of the ventricle, therefore, must lead to an elevation of the apex forward and upward,¹ because the base of the organ is naturally more firmly anchored than its apex (Fig. 141). Thirdly, this upward kick of the ventricle is intensified by the fact that the apex turns slightly around its longitudinal axis, bringing a more extensive portion of its left side into view.²

¹ W. Harvey, "*Cor sese erigere.*"

² W. Harvey, "*lateralem inclinationem.*"

In accordance with the observations made upon the excised heart, it may seem surprising that the changes in the different diameters of the heart do not cause the apex to be displaced in an almost straight line upward toward the base. Different reasons may be given for its relative immobility. While it must be granted that the heart is more firmly anchored at its base on account of the firm support afforded it by the large blood-vessels, it must be remembered that the pericardial sac, together with its mediastinal fastenings to the diaphragm, possesses the tendency of counteracting any distinct displacement of the apex. It is also claimed that the discharging heart suffers a recoil in the manner of a cannon on being fired,¹ and secondly, that the sudden distention and straightening out of the aorta and pulmonary artery by the escaping ventricular blood causes the basal region to recede somewhat in a downward direction. The ventricle being thus opposed by a resistance above, must remain in its former position.²

FIG. 142.—CARDIOGRAPH.

This is strapped around the chest, the central button is applied to the "apex-beat" and its pressure on the chest wall regulated by means of the three screws at the sides. The tube at the upper part of the instrument serves to connect the drum of the cardiograph with a registering tambour, such as is shown in Fig. 143. (*Sanderson.*)

The Cardiogram.—A graphic record of the cardiac impulse or apex beat may be obtained with the help of two Marey tambours, one of which is fastened to the surface of the chest (Fig. 142) in the area previously designated, and the other upon a stand in relation with the smoked paper of a kymograph (Fig. 143). When connected by means of rubber tubing, the membranes of these tambours must oscillate in unison. If the membrane upon the receiving tambour is pressed inward by the bulging chest wall, the writing lever attached to the recording drum must move upward, and *vice versa*.

This instrument is known as the cardiograph, and the record made by it as the cardiogram. Not much importance can be attached to it

¹ Skoda, *Abh. über Perc. und Auskultation*, Wien, 1847, also see: Feuerbach, *Pflüger's Archiv*, xiv, 1877.

² Séna, *Traité de la struct. du coeur*, Paris, 1849, or Aufrecht, *Deutsch. Arch. für klin. Med.*, Nr. 19, 1877.

as a means of diagnosis, because it frequently fails to represent the conditions as they actually are. It must be granted, however, that the fault does not always lie with the instrument, but more frequently with the experimenter. If properly applied, it registers the different beats with accuracy, but does not allow definite conclusions being made regarding the character of the contractions, because its mechanism is easily affected by various factors such as changes in the position of the body, or alterations in the resistance under which it is made to act.

FIG. 143.—MAREY'S TAMBOUR.

a, Axis of lever; *b*, metal tray covered with rubber membrane, and communicating by tube *f* with the receiving drum shown in Fig. 142. (*Starling*.)

Moreover, the conspicuousness of the impulse differs even in perfectly normal individuals, owing to differences in the thickness of the chest wall.

Under ordinary conditions, the cardiogram consists of a series of upstrokes and downstrokes. The former indicate the successive systolic and the latter the successive diastolic movements of the ventricles. In complete agreement with the general character of the contraction of the cardiac muscle, these two limbs of the curve are generally joined

FIG. 144.—CARDIOGRAM.

AB, Systole; *BC*, plateau; *CD*, diastole; *DA*, pause; time in seconds.

by a "plateau," the implication being that this muscle does not relax immediately upon having attained its state of maximal shortening, but remains in this condition for a brief period of time. The curve may also present an initial slight rise which is caused by the systole of the auricles, and a small peak upon its downstroke which occurs synchronously with the closure of the semilunar valves.¹

¹ For purposes of diagnosis, it is necessary to ascertain not only the location of the impulse but also its strength. A displacement of it is brought about by accumulations of air (pneumothorax), serum (hydrothorax), blood, and pus, as well as by tumors of the thoracic and abdominal viscera. Hypertrophy and

B. THE ELECTRICAL VARIATIONS

The Action Current of the Heart. Electrocardiography.—The activity of any form of living substance is accompanied by the production of electrical energy. We have found this to be true in striated as well as in smooth muscle tissue. Cardiac muscle forms no exception to this rule, because, if the heart of a frog or turtle is exposed to the view and the nerve of a gastrocnemius preparation is placed upon it, the muscle is seen to twitch with every systole. In this particular case, the heart acts as a battery, and generates an impulse in the adjoining nerve which then causes the muscle to contract. The electrical current generated by the beating heart may be registered by means of suitable instruments, such as the capillary electrometer, or the galvanometer. Thus, if the two terminals of the former are placed upon the active organ, preferably upon its base and apex, the meniscus of the mercury in the capillary tube moves first in one direction and then in the other in synchronism with the successive periods of activity. The same result may be obtained with the help of the galvanometer, the reflecting mirror of this instrument being doubly deviated with each contraction.

The current rendered recognizable by this means is known as the current of action of the heart. It is dependent upon the fact that the active portion of this organ is electronegative to the resting portion. Inasmuch as the cardiac contractions begin at the base, this particular area of the heart is of a lower electrical potential than its still inactive apical portion. A moment thereafter, however, conditions are reversed. The apical region now having been activated, exhibits a galvanometric negativity, while the basal zone which is in the state of rest at this very time, becomes electropositive. In perfect analogy with skeletal muscle, the action current of the heart exhibits a diphasic character. This is indicated very clearly by the deflections of the indicator of the recording instrument which occurs first in one direction and then in the other. It should be added, however, that this current is somewhat different from the ordinary action current of skeletal muscle, its peculiarities being no doubt attributable to the much greater complexity of the cardiac musculature. These electrical changes are developed with great rapidity, so that the capillary electrometer and the ordinary type of galvanometer are not sufficiently motile to follow the different phases of this wave with accuracy. This difficulty has been almost entirely overcome by the very sensitive string galvanometer, invented by Ader¹ and modified by Einthoven.² The indicator of this instrument is a filament of quartz or platinum covered with a thin coating of silver and suspended between the poles of a powerful

dilatation of any part of the heart also change its position. The strength of the apex beat is indicative of the condition of the cardiac musculature, but only when the factors previously enumerated have been properly controlled.

¹ *Compt. rend., Ac. Sci., Paris*, cxxiv, 1897.

² *Ann. der Physik*, xii, 1903, and *Pflüger's Archiv.*, cxxx, 1909, 287.

electromagnet. The deviations which the string of this instrument suffers in the course of each cardiac cycle, may be projected and photographed upon sensitive paper moved with proper rapidity. The record so obtained is known as the electrocardiogram, and the complex apparatus necessary to take these tracings, as the electrocardiograph.

This method of studying the character of the cardiac contractions has attracted much attention in recent years; in fact, it has been so highly developed that it may be employed as an important diagnostic aid in ascertaining the functional capacity of even the human heart. While the currents produced by this organ are of very moderate strength, the modern type of electrocardiograph has been rendered sufficiently sensitive to detect them with ease. As Waller¹ has shown years ago, it is quite unnecessary to expose the heart to the view, because the current generated by it can be led off to the galvanometer by simply applying the terminals of this instrument to the integument. In the human subject, the electrodes are usually connected with the body in three ways, designated as leads, namely:

Lead I.—Right arm and left arm.

Lead II.—Right arm and left leg.

Lead III.—Left arm and left leg.

In the first case in which the two hands are connected with the poles of the string galvanometer, the right one may be regarded as the conductor which leads off from the base, and the left one, as the conductor which leads off from the apex of the heart.

Regarding the general outline of the normal electrocardiogram and the causes of its different minor phases, some uncertainty still prevails. Figure 146 represents the electrocardiogram most commonly obtained from normal human subjects. It is readily observed in the curve of Lead I that each cardiac cycle begins with a slight wave which has been designated by Einthoven as the P-wave (presystolic). Subsequent to this point, the string either retains its position of zero or is deviated somewhat below the base line. This primary deflection is due to the contraction of the auricles and is spoken of, inclusive of the presystolic,

FIG. 145.—DISTRIBUTION OF POTENTIAL DIFFERENCES DUE TO ELECTRICAL VARIATIONS IN THE BEATING HEART. (Waller.)

To record the variations any of the points *a* may be led off, together with any of the points *b*.

¹ Philo. Transact., 1889, 180.

as the "auricular complex of the electrocardiogram."¹ The "ventricular complex" of the curve is much more complex. When fully developed, it consists of a deflection below the abscissa, called the Q-wave, a very conspicuous upward deviation or R-wave, a second depression or S-wave, and a broad rounded elevation or T-wave. The largest variation at R consumes 0.02 to 0.04 sec. and the one at T, 0.1 sec. The total time of this complex corresponds approximately to the duration of the ventricular contraction, which has been proved

FIG. 146.—ELECTROCARDIOGRAM OBTAINED BY PHOTOGRAPHING THE MOVEMENTS OF THE THREAD OF A STRING-GALVANOMETER.

The upper figure shows the photographed curve while the lower one is a diagram constructed from the photograph to show the electrical changes occurring during a single cardiac cycle. To obtain this record the electrodes were connected with the right and left hands. Waves with the apex upward indicate that the base of the heart (or the right ventricle) is negative to the apex (or left ventricle). Waves with the apex downward have the opposite significance. Wave *P* is due to the contraction of the auricle. Waves *Q*, *R*, *S*, and *T* occur during the systole of the ventricle. The curve seems to show that the contraction in the ventricles begins first toward the apex (or in the left ventricle), since the negativity first appears toward that side (wave *Q*). (*Einthoven*.)

to begin very shortly after the onset of the deflection at *R* and to continue to about the end of the *T*-wave.

A detailed discussion of the individual variations in the electrocardiogram² cannot prove of much value, because many matters pertaining to it must first be thoroughly investigated. Its complexity, however, clearly betrays the segmental arrangement of the cardiac musculature as well as the wave-like character of its contraction. It appears that the excitation wave, on being distributed to the different areas of the heart, gives rise to a muscular activity which is not at all

¹ Lewis, Clin. Electrocardiography, London, 1913.

² Einthoven, Pflüger's Archiv, cxlix, 1913, 65; Meek and Eyster, Am. Jour. of Physiol., xxx, 1912, 271; James and Williams, Am. Jour. of the Medical Sciences, 1910, and Kraus and Nicolai, "Das Electrocardiogram," Leipzig, 1910.

simultaneous. For this reason, the different zones of the cardiac musculature must present different electrical potentials toward one another. As far as the significance of the general details of the electrocardiogram are concerned, it might be mentioned in brief that an auricular complex of the form previously described, indicates that the wave of excitation arises in its proper place at the venous vestibule and is propagated in normal sequence through the whole of the auricular tissue. As far as the ventricular complex is concerned, it should be noted that the deviations at R and T are always present in normal records and that the deflections at Q and S differ greatly in amplitude. Their presence signifies that the auricular impulse has traversed the auriculo-ventricular bundle and its ramifications in a proper manner and direction. Age usually lessens the conspicuousness of the T-wave, while exercise increases it. Curiously enough, the electrocardiogram secured from the hearts of the lower forms, coincides very closely with that obtained in mammals.

C. THE HEART SOUNDS

First, Second and Third Sounds.—All contracting muscle tissue emits a sound, which is caused by the molecular shifting of its substance and the displacement of its fibers. The intensity of this sound must therefore be proportional to the mass of the tissue involved as well as to its power of contraction. In the case of the heart, three additional factors must be taken into account, namely (a) the play of the fibrous flaps forming the valves, (b) the friction of the blood upon the endocardial lining of the narrowed orifices, and (c) the friction of the organ as a whole against the chest wall and neighboring viscera. Clearly, therefore, the sounds heard in the region of an active heart may be said to be of intracardiac and extracardiac origin.¹ While both types deserve recognition, the former are of much greater physiological importance.

If the unaided ear is applied to the surface of the chest in the region of the heart and preferably over its apex, two very distinct sounds are heard during each cardiac cycle which may be represented phonetically by the syllables "lubb-dup" or tā-tă. The first possesses a rather low pitch and is fuller and longer than the snappy and sharp second sound. They may be rendered more audible by means of resonators, such as are contained in some of the monaural or binaural forms of *stethoscopes*. But if an instrument of this kind is employed, a certain care must be exercised, because diverse errors in auscultation may arise in consequence of poorly fitting ear pieces, or in consequence of the improper application of the bell-shaped receptor to the thorax.²

¹ Noises are frequently heard in other parts of the vascular system, generally at the points where the channels deviate from their former course or are constricted. Venous bruits are not at all uncommon.

² The cardiac sounds are modified in their intensity by any factor (respiratory movements, pulmonary infiltrations, pericardial effusions, etc.) producing a change

The cardiac sounds have been recognized at an early date. Harvey, for example, states that the delivery of a quantity of blood into the arteries produces a pulse which can be heard within the chest, but Laennec¹ was the first to describe the character of the sounds and to make use of them for clinical purposes. Graphic records of them have been obtained by Donders (1856), Martin (1888) and Hürthle (1892), but the first really satisfactory method of registration has been devised by Einthoven and Geluk.² The sounds transmitted by a stethoscope were caught upon a microphone. The currents were then led off to a capillary electrometer, and photographed by projecting the movements of the mercurial column of this instrument upon sensitive paper moved with a certain velocity. In recent years, this means of registration has been displaced by the string galvanometer. Frank³ has devised an instrument without a microphone, the sounds being transferred directly from a stethoscope onto a membrane carrying a reflecting mirror. It should be mentioned, however, that the records so obtained are not always satisfactory, because they really represent a combination of phonogram and cardiogram. Under ordinary conditions, however, it is not difficult to differentiate between the rapid oscillations caused by the cardiac sounds, and the slow deflections produced by the contraction of the cardiac musculature. By means of the method described previously, Einthoven⁴ has succeeded in registering a third heart sound which, however, cannot usually be heard with the stethoscope.

The first sound occurs during ventricular systole. It begins with the "setting" of the ventricles and continues until the highest intraventricular pressure has been produced. This point coincides with the beginning of the plateau, when the semilunar valves are forced open. It is loud at first, but becomes less intense toward the end of the ventricular contraction. It lasts 0.07 to 0.10 sec.

It may be concluded that the first sound of the heart is due very largely to the friction noises emitted by the contracting ventricular musculature,⁵ because:

(a) It is also produced by the exposed and bloodless heart, and also by excised portions of the ventricle and by apex preparations.

(b) The sound begins before the closure of the auriculoventricular valves and continues practically throughout ventricular systole until the muscle fibers have attained their maximal degree of shortening.

in the tissue situated between the heart and the chest wall, as well as by structural alterations in the musculature of the organ itself (hypertrophy and dilatation). Moreover, when one or several of the valves become incompetent, the resulting murmurs seriously impair the normal character of these sounds.

¹ De l'auscultation, Paris, 1819.

² Pfüger's Archiv, lvii, 1894, 617.

³ Kongr. für inn. Med., Wiesbaden, xxv, 1908; also see: Weiss, Das Phonoscope, Med. nat. Arch., Berlin and Wien, i, 1908.

⁴ Pfüger's Archiv, cxx, 1907, 31.

⁵ C. J. B. Williams, Rep. Brit. Assoc. for the Adv. of Science, London, 1836.

(c) The auriculoventricular valve flaps may be hooked back without markedly impairing the quality of the sound.

(d) The character of the sound is decrescent.

(e) The contracting auricles also emit a sound which, however, remains below the threshold of audibility, owing to the small mass of tissue involved.

It is generally conceded, however, that the first sound also contains a slight valvular element, because if the play of the valve flaps is restricted or prevented, it displays a somewhat different character. We know that the ventricular systole insures first of all the closure of the auriculoventricular valves (Fig. 147 *a*), and shortly thereafter, the opening of the semilunar valves (*b*). As the outward movement of the latter is accomplished practically without noise, it must be concluded that the modification imparted to the muscular element of the first sound must be dependent upon the initial contact and the subsequent after-vibration of the closed mitral and tricuspid valves.

FIG. 147.—SCHEMA TO SHOW THE RELATIONSHIP BETWEEN THE HEART SOUNDS AND THE CURVE OF INTRAVENTRICULAR PRESSURE.

AB, systole; *BC* plateau; and *CD*, diastole; *a*, closure of auriculoventricular valve; *b*, opening of semilunar valve; *c*, closure of semilunar valve; *d*, opening of auriculoventricular valve; *I*, *II* and *III*, heart sounds.

The second sound occurs at the beginning of ventricular diastole and follows immediately upon the closure of the semilunar valves. It lasts 0.05–0.11 sec., while the interval between it and the first sound amounts to 0.15–0.25 sec. It is most intense when the blood pressure is high and when the arterial system is very elastic.

In contradistinction to the first sound, the second sound possesses no muscular element. It is purely valvular in its origin and is caused by the tension and after-vibration of the closed semilunar valves. This can be shown in the following way:

(a) If the tension in the aorta and pulmonary artery is lessened by permitting a quick escape of the arterial blood, the intensity of the second sound is greatly diminished.

(b) If the heart is rendered bloodless, it ceases to give a clear second sound.

(c) If the semilunar valve-flaps are hooked back, the second sound gives way to a murmur, due to the regurgitation of the blood into the ventricular cavity.

(d) A sound very similar in character to the second sound may be produced in

an excised segment of aorta by quickly forcing a column of water through the semilunar orifice toward the ventricular cavity.

The third sound is diastolic in its nature and occurs 0.13 sec. after the beginning of the second. It is soft and low in pitch. Two causes have been assigned to it. As it appears to follow in the wake of the second, Einthoven has suggested that it is dependent upon the after-vibration of the closed semilunar valves. It is also claimed that it is due to the vibration of the auriculoventricular valves¹ which are opened at this moment of diastole, and to the friction-noises occasioned by the blood as it rushes into the ventricles (*d*).

D. THE CHANGES IN INTRACARDIAC PRESSURE

THE FILLING OF THE HEART

Methods of Registration.—By the term intracardiac pressure is meant the pressure to which the blood is subjected while traversing the different chambers of the heart. To begin with, it is to be noted that the general character of the pressure variations in the auricles is quite different from that of the variations taking place in the ventricles, but that the two ante-chambers as well as the two main chambers show an almost complete correspondence. In addition it should be remembered that the former develop equal degrees of pressure, while the latter do not, because the pressure encountered in the left ventricle, is much higher than that prevailing in the right.

FIG. 148.—SCHEMA TO ILLUSTRATE THE METHOD OF RECORDING THE BLOOD PRESSURE IN THE RIGHT AURICLE AND VENTRICLE.

A probe (*S*) filled with saline solution, is inserted through the ext. jug. vein. The tambour (*T*) registers the pressure upon a kymograph (*K*). The connecting tubing is equipped with a stop-cock or clip (*C*).

The methods employed to determine the intracardiac pressures may be arranged in two groups, the first embracing those procedures which are practicable only when the heart is fully exposed to the view, and the second, those which are also practicable when the chest is still closed. In the first instance, the cardiac chamber is connected directly with a manometer. Entrance to the auricular cavity is effected

through its appendage into which a cannula may be inserted without causing the slightest disturbance in the heart's action. The right auricular cavity may also be reached by introducing a hollow probe through the superior vena cava, and the left cavity by introducing

¹ Thayer and Gibson, Boston Med. and Surg. Jour., 1908.

a tube through one of the pulmonary veins. The same procedures may be followed in the case of either ventricle. A pointed tube attached to a manometer is forced slantingly through its wall. This method does not entail a loss of blood, because the musculature closes firmly around the tube. With the chest closed, the right auricle and ventricle may be explored with the aid of a long catheter which is introduced through the right external jugular vein (Fig. 148). A regurgitation of the blood into the auricle does not result under these circumstances, because the tricuspid flaps close tightly around the tube. With the chest intact, the left ventricle may be rendered accessible to the recording instruments by means of a slender probe which is inserted through the left carotid artery and the aorta. As holds true in the case of the tricuspid valve, the semilunar flaps attach themselves firmly to the tube so that a serious regurgitation cannot result. The chest remaining closed, the left auricle is not accessible to manometric measurements, but the pulsations of its wall may be registered by means of a small rubber bulb which is advanced through the esophagus until it reaches the level of this cavity.

The Mercury Manometer.—The determination of the pressure developed in the different compartments of the heart, may be effected with the help of an indicator commonly designated as a manometer. This instrument has been developed in two directions, its two forms being known as the mercury manometer and the membrane manometer. For the present we shall confine ourselves to a consideration of the construction and method of application of the former instrument. In its earliest form it consisted of a perfectly straight tube which was filled with water, the pressure being indicated by the height of the column of water. Later on U-shaped tubes were used as a matter of convenience. A still more practical form was given to this instrument in 1828 by Poiseuille, who displaced the water by mercury. As the latter possesses a specific gravity 11.7 times greater than that of blood and 13.55 times greater than that of water, the limbs of the U-shaped glass tube could be materially shortened without diminishing the range of this instrument. Another important modification consisted in filling the connecting tube between the manometer and the blood-vessel with an anticoagulating agent, for example, with a concentrated solution of sodium bicarbonate or magnesium sulphate. But, when testing the pressures within the chambers of the heart, it is best to use normal saline solution, because the leakage of even an inconsiderable quantity of the aforesaid fluids into the circulation is prone to produce undesirable results. To avoid this possibility Marey and Chaveau employed a catheter, the free end of which was closed with a delicate rubber membrane.

The displacement of the column of mercury in the U-shaped tube may be read off directly or may be recorded upon the paper of a kymograph in the manner described by Ludwig (1847). A float of hard rubber is placed upon the mercury in the distal limb of the manometer. The float in turn is equipped with a vertical

rod which carries a writing outfit. The latter consisted originally of a small capillary glass pen which was connected with a tiny receptacle filled with ink. The record was made upon white paper revolved with a certain speed. At the present time, however, smoked paper is used most frequently, the writing needle consisting simply of a delicate crosspiece situated upon the free end of the vertical rod.

One difficulty encountered in registering changes in pressure is presented by the great inertia of the mercury. In the heart, the fluctuations are extreme and are developed with such rapidity that the mercury is quite unable to follow them accurately. To begin with, its sluggishness causes it to lag behind, while when once set in motion, it tends to continue in the same direction, surpassing the actual pressure, often very considerably. For this reason, it is practically im-

FIG. 149.—SCHEMA TO SHOW THE CONNECTION MADE BETWEEN THE ARTERY AND MANOMETER.

M, manometer; *H*, mercurial column; *F*, float; *D*, recording needle; *K*, kymograph; *B*, tube leading to reservoir filled with solution of sodium carbonate; *R*, rubber tubing filled with sodium carbonate solution; *C*, glass cannula in artery; *A*, clip upon artery; *V*, maximal-minimal valve (Frank) to be inserted in this circuit; 1, maximal side; *V*₁, maximal valve of Hürthle. A minimal valve is obtained by inverting the central tube.

possible to obtain an exact record of the intracardiac pressures by means of this instrument. It may be used, however, to register either the lowest or highest degrees of pressure, as well as the mean pressure. To accomplish this end, a so-called maximal-minimal valve must be interposed between the heart and the manometer.¹ In its simplest form this valve consists of a short cannula which is surrounded by a wide jacket of glass (Fig. 149 *V*₁). The free end of the cannula is bevelled and is equipped with a flap of rubber membrane fastened to it in the manner of a door. As the different waves of systolic pressure traverse the cannula this flap is raised, so that the column of mercury in the manometer is constantly forced upward until it accurately counterbalances the pressure. At this level it is

¹ Hürthle, Pfüger's Archiv, xliii, 1888, 399.

held, because a movement in the opposite direction is prevented by the immediate approximation of the flap to the mouth of the cannula. Quite similarly, the diastolic minimum may be determined very easily by inverting the glass cannula so that its outlet is now directed toward the heart. The mercury is then drawn downward until it approximates the lowest pressure prevailing in the heart. The mean pressure may be obtained by interposing in the system of connecting tubes a stop-cock which is closed more and more until the mercurial column eventually shows only the smallest possible oscillations.

As the pressure in the auricles is low, the manometer tube should be filled with water instead of mercury. The displacement of the water, however, should always be given in millimeters of mercury, because blood pressures in general are usually adjusted to this standard. The exact height of the pressure registered by the manometer at any one moment is obtained by measuring the distance (H) between the zero line, or abscissa, and the level of the curve recorded by the writing needle of the float. This distance must then be multiplied by two, be-

FIG. 150.—DIAGRAM TO SHOW THE ADJUSTMENTS NECESSARY FOR DETERMINING THE ZERO-LINE OF THE MANOMETER (M).

Its central limb (A) is brought upon the same horizontal line as the level of the water in the glass bulb (B) when held at the level of the blood vessel (C).

cause the tube is U-shaped, *i.e.*, while the column of mercury moves upward in its distal limb, it moves downward in its central limb. The float, of course, indicates solely the movement of the distal limb of the mercury, *i.e.*, one-half of the total movement of the mercurial column. Another factor must also be taken into consideration, namely the specific gravity of the fluid against which the blood pressure is exerted. As mercury possesses a specific gravity which is 13.5 times greater than that of blood, the height of the column of mercury (H) must be divided by 13.5. The figure so obtained must then be subtracted from the preceding value. The complete formula for calculating the blood pressure is as follows:

$$Pr = 2H - \frac{H}{13.5}$$

It need scarcely be mentioned that the zero line must be accurately determined beforehand by temporarily connecting the manometer with a glass bulb containing water. When the level of the water is approximated to that of the mercury in the central limb of the instrument, the float is adjusted at zero. The blood-vessel in which the pressure is to be ascertained, must, of course, be approximated to the level of the mercury in the central limb of the manometer (Fig. 150).

Systolic, Diastolic and Mean Pressure.—The pressure in the chambers of the heart undergoes extreme variations during each cardiac cycle. The lowest values are reached at the end of diastole and the highest at the end of systole. Thus, the pressure in the left ventricle rises in the course of 0.06 sec., from near zero to about 130 mm. Hg. The former is called the diastolic and the latter the systolic pressure. For ordinary purposes it suffices to calculate the average pressure by simply obtaining the arithmetical mean between the diastolic and systolic values. It is essential, however, to include a considerable number of cardiac cycles in this calculation.

The Membrane Manometer.—The tendency has been in recent years to procure an instrument which is capable of following the rapid alterations in pressure without that its parts, when once displaced, enter into vibrations of their own. It is desirable at all times to obtain not only the extreme heights of the pressure, but also its intermediate values; in other words, it is of importance to secure a complete trac-

FIG. 151.—DIAGRAM OF MEMBRANE MANOMETER.

M, rubber membrane connected with writing lever (*L*). The drum (*T*) is connected with the cannula in the blood vessel; *R*, rod to fasten manometer to stand.

ing of the curve of pressure. This end has been attained with a fair degree of accuracy by means of elastic manometers in which the pressure is not counterbalanced by the weight of ordinary liquids, such as water and mercury, but by the resistance resident in an elastic body. A rubber disc or a metal spring are usually employed for this purpose.

The simple membrane manometer designed by Hürthle,¹ consists of a metal drum closed by a sheet of thin rubber, the excursions of which are transferred directly to a writing lever (Fig. 151). The sensitiveness of this instrument has been much increased by permitting the membrane to act against a steel spiral which in turn is connected with a writing lever. This principle is embodied in the so-called spring, torsion, and reflecting or optical manometers. In all of them the variations in the pressure of the blood are transmitted through the column of the fluid contained in the connecting tubes, to the rubber membrane of the manometer. The displacement suffered by the latter in consequence of the transferred pressure is recorded in magnified form upon the paper of a kymograph. An instrument of this kind must be calibrated repeatedly, *i.e.*, the excursions of its rubber membrane, as indicated by the writing lever, must be compared with the movements of a column of mercury so that they may be expressed in terms of millimeters of mercury.

¹ Pflüger's Archiv, xlix, 1891, 29. The first elastic manometer was constructed by Fick in 1864 in compliance with the metal manometer of Bourdon.

The manometers designed by O. Frank¹ do not differ materially from those devised by Hürthle. The principle involved in their construction is that the mass of liquid actually moved for the purpose of transferring the blood pressure, must be as small as possible, otherwise the momentum of the different parts of the instrument may give rise to vibrations which are not at all in keeping with the conditions as they actually are. The tendency to "after-vibrate," Frank has sought to mitigate by making the connecting tube between the blood-vessel and the manometer as large and as short as possible, while the orifice carrying the recording membrane is reduced to the smallest size practicable (Fig. 152). The frequency of vibration of this instrument is extremely great and hence its power of accurately following the variations in pressure cannot be doubted. Without desiring to enter into a detailed discussion of the theory of manometers, it may be stated that Hürthle does not regard the principle as put down by O. Frank as physically sound.² Naturally, the greatest sensitiveness is attained by the reflecting or optical manometer. The membrane of this instrument is not weighted by a writing lever with its different adjustments, but is equipped solely with a very small mirror

FIG. 152.—DIAGRAM OF FRANK'S MEMBRANE MANOMETER.

K, for attachment of cannula inserted in blood vessel; *bde*, connecting piece of manometer filled with sodium carbonate solution; *cf*, connections for flushing out the system; *S*, membrane; *S*, mirror riding upon membrane.

from which a beam of light is reflected against a screen. In this way, the oscillations of the membrane may also be transferred upon the sensitive paper of a camera moved with a certain rapidity.

The Intra-Auricular Pressure and the Function of the Auricles.—If the cavity of the right auricle of a dog is connected with a maximal-minimal valve and with a mercury manometer, it will be found to produce a systolic pressure of about 20 mm. Hg. and a diastolic pressure of -10 to -20 mm. Hg.³ The total change in pressure in this chamber, therefore, amounts to 30 or 40 mm. Hg. during each cardiac cycle. Very similar conditions prevail in the left auricle. It may be stated at this time that the negative pressure encountered in these cavities, as well as in the central venous trunks, is not developed actively, but is dependent upon the aspiratory action of the tissue of the lungs. These organs exert an elastic pull upon the relatively soft walls of these

¹ Zeitschr. für Biologie, 1910, 53.

² Pfäfer's Archiv, cxxxvii, 1911, 225.

³ Goltz and Gaule, *ibid.*, xvii, 1878, 100.

venous compartments, in consequence of which the blood within them is placed under a lower pressure than it would be otherwise. The veins outside the thorax, on the other hand, are exposed to the atmospheric pressure. Obviously, therefore, this negative pressure in the central part of the circulatory system must disappear immediately upon opening the chest, because the ensuing collapse of the lungs nullifies their elastic pull upon the blood-vessels. The opposite effect may be produced under normal conditions by raising the intrathoracic pressure, as may be done by holding the breath or by making forced expiratory movements. A far-reaching venous engorgement and arterial deficiency may thus be incited, which are indicated, on the one hand, by the swelling of the superficial veins and, on the other, by the lessened amplitude of the arterial pulse. Obviously, this rise in the venous pressure must be associated with a lessened filling power of the auricles, because the relaxation of these parts is then greatly hindered by the pressure resting upon their outer surfaces:

If a continuous record is made of the changes in the intra-auricular pressure with the help of an elastic manometer, the curve so obtained

FIG. 153.—THE CURVE OF INTRA-AURICULAR PRESSURE.

AB, systole; BD, diastole; DA, pause; C, second summit; E, third summit.

presents the details indicated in Fig. 153. The systolic period of the auricle occurs between A and B, and the diastolic between B and D. Between this point and the beginning of the next cardiac cycle (DA) the auricle is said to be at rest. The wave as a whole exhibits three elevations, namely, one each at B, C and E. The first, no doubt, is due to the contraction of the auricle, and indicates the point of maximal intra-auricular pressure. The second summit (C), interrupts the steady fall in pressure accompanying the relaxation of the auricular musculature (BD). Its cause is to be sought in the slight upward displacement of the auriculoventricular septum occasioned by the contraction of the ventricles. The size of the auricular cavity is somewhat diminished thereby, causing the pressure to rise. The third elevation (E) is dependent upon the quick inrush of venous blood which results as soon as the auricular wall becomes passive. This rather abrupt initial rise soon gives way to a more gradual one, as the auricles become filled. The auriculoventricular valves are forced open at E. A certain quantity of blood then escapes into the now diastolic ventricles. This

change permits of an equalization of the pressures, so that the filling may take place more slowly. This period is indicated in the diagram by the letters *E* and *A*, the latter marking the beginning of the subsequent auricular systole.

As the orifices of the *venæ cavæ* and pulmonary veins are not guarded by valves, the variations in intra-auricular pressure must necessarily be propagated outward into the adjoining venous trunks. They appear here in the form of the physiological venous pulse.¹ In accordance with the preceding discussion, it must also be evident that an incompetency of either the tricuspid or mitral valve must occasion a much greater second rise in the intra-auricular pressure than is present under normal conditions. This must be so because the auriculoventricular flaps now not only encroach upon the space of the auricles, but permit a certain quantity of ventricular blood to escape into these cavities. The summit at *C* is then rendered more conspicuous, until, in severe types of insufficiencies of these valves, it completely obliterates the first elevation (*A* to *B*). This condition gives rise to a similar modification of the physiological pulse in the central veins, the second elevation increasing in size until it becomes almost confluent with the first. It is then known as the pathological venous pulse.

The **filling of the auricles** is accomplished during the intervals between the successive rises in intra-auricular pressure. It has been shown by Burton-Opitz² that the influx of blood is rapid during early diastole (*B* to *C*), but is much diminished during the rise in pressure occasioned by the upward bulging of the auriculoventricular septum (at *C*). Immediately following this phase, another rapid inrush of blood results (*C* to *D*), which, as has been stated above, is responsible for the third summit upon the curve of intra-auricular pressure. During the subsequent pause (*E* to *A*), the flow becomes slower and slower until it again ceases during the next systole (*A* to *B*). It will be seen, therefore, that the venous blood enters the auricles at a time when their musculature is at rest, and hence, it may be inferred that the influx of the blood into the auricles, or the filling of the heart, is occasioned passively by the circumstance that the pressure prevailing in the central veins, is higher than that existing in the diastolic auricular cavities.

The auricles serve as storehouses for the ventricles, because they hold a certain quantity of blood in readiness until the very moment when they must deliver it to the ventricles. But the dynamical conditions in the vascular system are subject to considerable variations, and hence, the quantity of blood which must be accommodated by them, is not always the same. Owing to their very distensible appendages, the auricles are structurally well fitted to adjust themselves to

¹ A more detailed discussion of the venous pulse will be found upon page 388.

² Am. Jour. of Physiol., vi, 1902, 435.

varying quantities of blood. The ventricles, on the other hand, are much more compact and cannot be made to yield so readily. It should also be emphasized that the auricles do not simply store the blood in a passive way, but also develop a driving force sufficiently high to fill the ventricles to their utmost capacity. The pressure values cited previously, however, prove that the power developed by them is relatively slight, but inasmuch as they discharge their contents into the ventricles at a time when the latter are at rest, practically no resistance need be overcome by them. We have seen that the inflowing venous blood opens the auriculoventricular valves sometime before the systolic movement of the auricles actually begins. This enables a moderately large quantity of blood to escape into the ventricles even before the onset of the next auricular systole. Consequently, all the latter needs to accomplish is to force in an additional amount so that the ventricle becomes fully distended. Their duty is, so to speak, to ram the charge home.

The Intraventricular Pressure and the Function of the Ventricles.—

The determinations with the maximal-minimal manometer have proved that the pressure in the ventricles is subject to much greater variations than the pressure in the auricles. In the second place, it has been found that by far the greatest power is developed by the left ventricle, which fact is in perfect agreement with the extraordinary thickness of its walls. Obviously, an unusually high driving force is necessary to propel the blood through the channels of the systemic circuit. Thus, while the systolic pressure in the left ventricle of the human heart amounts to about 125–140 mm. Hg., the right ventricle develops a pressure of scarcely more than 50 mm. Hg. Much higher values, however, are obtained whenever the circulatory mechanism is called upon to perform an extra amount of work. For example, one of the most efficient means of raising the intraventricular pressure, as well as the general blood pressure, is muscular exercise.

During diastole, the pressure falls to within a few millimeters of zero. In fact, a slight negative pressure has been encountered at times in certain hearts, but as this result is not constant, its cause must be sought in certain accidental conditions, rather than in an active relaxation of the cardiac musculature. This conclusion finds confirmation in the fact that an elastic recoil, such as is possessed by a rubber-bulb, has not been observed in the case of the heart. Moreover, it has been shown that a normally beating organ is unable to derive its supply of blood from a U-shaped tube adjusted at its own level.¹ In addition, Porter² has proved that the negative pressure in the ventricles is not associated with a corresponding fall in the intra-auricular pressure, and hence, it may be inferred that the venous column without is not subjected to an actual suction action. Several explanations have been offered for this occasional negative pressure.

¹ Von den Velden, *Zeitschr. für exp. Path. und Ther.*, iii, 1906.

² *Jour. of Physiol.*, xiii, 1892, 513.

Thus, it has been suggested that the sudden cessation of the ventricular systole forces the column of blood onward with a certain momentum, while in the wake of it is developed an area of very low pressure. The second and more probable explanation takes into account the fact that the sudden discharge of the ventricular contents gives rise to an abrupt distention of the trunks of the aorta and pulmonary artery which in turn leads to an expansion of the basal portion of the heart, inclusive of the adjoining extent of the ventricle. This effect is especially evident in the left cavity, because its wall is more compact and relatively unyielding. In an experimental way this condition may be imitated by suddenly distending the roots of the aorta and pulmonary artery with fluid, while the intraventricular pressure is being registered by a mercury manometer which is connected with this cavity by means

FIG. 154.—THE CURVE OF INTRAVENTRICULAR PRESSURE.
AB, systole of ventricle; BC, plateau; CD, diastole; DA, pause.

of a trocar inserted directly through its wall. Every distention then gives rise to a negative pressure.

The systole of the ventricle is indicated in Fig. 154 by the abrupt rise occurring between A and B. The normally beating ventricle, however, does not relax immediately upon the completion of its contraction but remains in this condition for a brief period of time. We observe, therefore, that the maximal value of the pressure is maintained and that the summit of the curve is flat. The "plateau" so formed¹ is indicated in the figure by the letters B and C. The subsequent relaxation of the ventricles occurring between C and D, is accompanied by a rapid fall in pressure. During the pause the pressure rises very slowly, owing to the gradual influx of blood through the just barely opened auriculoventricular valves. As has been stated above, the ventricles are filled for the most part before the succeeding auricular contraction actually begins, so that the latter merely serves the purpose of adding a certain extra amount of blood.

¹ The claim has recently been made by Straub that the summit is pointed; Hürthle, however, has proved this view to be erroneous.

Clearly, the function of the ventricles is to develop the pressure necessary to drive the blood through the vascular system. They impart kinetic energy to the blood, and naturally, as the resistance in the general circuit is much greater than that in the pulmonary circuit, the left ventricle must produce a much higher pressure than the right. We have previously seen that the changes in intra-auricular pressure are propagated outward into the veins, where they appear in the form of the physiological venous pulse. In a similar manner, the intraventricular pressure makes itself felt throughout the arterial system, where it forms the basis of the arterial pulse, because each ventricular discharge raises the pressure in these channels above that prevailing during the diastolic period of the heart. This topic will be dealt with in greater detail in a subsequent chapter.

The *cardiac output* per unit of time varies directly with the frequency of the contraction and the power of filling of the ventricles. Approximate values may be obtained in several ways, namely by:

- (a) Calculation from the total amount of blood present in the body.
- (b) Measuring the capacity of the chambers of the excised heart.
- (c) Determining the volume-curve of the beating heart by means of the cardiometer.
- (d) Calibrating the aortic blood-stream of the normal or excised heart with the aid of a stromuhr, or current measurer.

In addition, Zuntz has devised an indirect method for determining this factor which depends upon a comparison of the amounts of oxygen in the respiratory air, and the differences in the oxygen content of the arterial and venous blood. To illustrate, a horse weighing 360 kilos uses 2733 c.c. of oxygen in a minute, and its arterial blood contains 10.33 per cent. more oxygen than its venous blood. Thus, as every 100 c.c. of pulmonary blood are charged with 10.33 c.c. of oxygen, and as in all 2733 c.c. of this gas are consumed in a minute, the total quantity of blood traversing the lungs must amount to:

$$\frac{100 \times 2733}{10.33} = 26,457 \text{ c.c.}$$

Assuming a cardiac frequency of 50 in a minute, each contraction of the right ventricle must yield about 50 c.c. of blood. Moreover, as the left ventricle works in perfect unison with the right, this figure must also represent the aortic discharge. Plesch states that the cardiac output amounts to 59 c.c., this value being based upon gasometric experiments upon man. By using the absorption of nitrous oxid gas as an index, Krogh¹ has found values ranging between 40 and 120 c.c. in accordance with the frequency of the heart. This author also states that muscular exercise increases the output very markedly. By following a similar analytical procedure, Boothby² has obtained an average value of 60 c.c.

¹ Skand. Archiv für Physiol., xxvii, 1912.

² Am. Jour. of Physiol., xxxvii, 1915, 383.

While the direct determination of the capacity of the ventricles of the excised heart presents no unusual difficulty, it cannot possibly yield exact results, owing to the changes in the tonus and elasticity of the musculature subsequent to the removal of the organ and our inability to reproduce the rhythmic changes in pressure under which the heart ordinarily works. The attempt has also been made to measure the cardiac output by determining the difference in the volume of the heart during its systolic and diastolic periods. Experiments of this kind have been performed by Stefani,¹ Knoll,² Johansson and

FIG. 155.—DIAGRAM OF ROY'S CARDIOMETER.

Tigerstedt,³ and others. They consisted in inserting a cannula into the pericardial sac, and in registering the volumetric changes by means of a suitable piston-recorder. But naturally, as even the slightest increase in the pressure in this pouch tends to hinder the relaxation of the heart, the resulting values cannot be said to be exact. Moreover, as the pericardial membrane also envelops the auricles, it cannot be avoided that the volumetric changes of this portion of the heart are transferred to the recorder together with those of the ventricles. Roy and Adami⁴ have employed round metal capsules, or cardiometers, consisting of two hemispherical shells, and large enough to contain the heart in its entirety. The space intervening between

¹ Archiv de le scienze med., iii, 1879, 7, and Arch. ital. de biol., xviii, 1892, 119.

² Sitzungsber. der Wiener Akad. d. Wissensch., 1881, 82.

³ Skand. Archiv für Physiolog., i, 1889, 345.

⁴ British Med. Jour., ii, 1889, and Phil. Transactions, clxxxiii, 1892, 199.

this organ and the metal capsule, was filled with oil and was connected with a piston-recorder by means of tubing. Under very favorable conditions the excursions of this instrument should correspond precisely to the variations in the volume of the beating heart. This result, however, is not obtained under ordinary circumstances, because even this type of cardiometer does not meet all the requirements of a perfect instrument of precision. Johannson and Tigerstedt have overcome these difficulties in a measure by employing a bulbular cap-

FIG. 156.—CARDIO-METER.

The heart is inserted through a perforation in rubber membrane (*R*) into cavity of a hemispherical glass capsule (*C*). The latter is connected with a recording tambour (*T*).

sule just large enough to envelop the ventricular portion of the heart. The round opening at its upper pole is closed by a rubber membrane with a central perforation through which the ventricle is inserted. Henderson¹ has made use of hemispherical capsules of glass, and of ordinary rubber balls cut in half. Great care must be exercised that the opening in the rubber membrane is not too small, otherwise the filling of the ventricles will be seriously impaired. Rothberger,² who has measured the ventricular discharge directly, finds that exact values cannot be obtained with cardiometers even under the most favorable conditions.

The attempt has been made by Burton-Opitz³ to calibrate the systolic discharge of the right ventricle with the help of a recording stromuhr, or current measurer. Piston and syphon recorders have been employed by Stolnikow⁴ and Starling.⁵ The systolic-diastolic changes in the beating heart can also be made out very clearly during transillumination of the chest by means of the Röntgen rays.

It may be said in a general way that a rapid heart discharges more blood in a given period of time than a slow one. This statement, however, does not hold true under all conditions, because it can readily be demonstrated that the ventricular output may vary even when the cardiac frequency remains the same, while, at another time, the output may remain practically unchanged in spite of the fact that the frequency of the heart is either increased or decreased. This result indicates that the cardiac output per unit of time is dependent not only upon the number of systoles, but also upon the quantity of blood ejected each time. As the latter factor represents the filling power or capacity of the heart, it must be evident that the relaxability of the

¹ Am. Jour. of Physiol., xvi, 1906, 325.

² Pfüger's Archiv, 118, 1907, 353.

³ Proc. Soc. for Exp. Biology and Medicine, 1903.

⁴ Archiv für Anat. und Physiol., 1886, i.

⁵ Jour. of Physiol., xlv, 1912, 164.

cardiac musculature is of as great importance as its force of contraction. Thus, a rapid heart may fail at times to eject a larger quantity of blood than a slow one, because the length of time allotted to it for its filling, is too brief. Quite similarly, a slowly beating organ may succeed at times in furnishing a perfectly adequate supply of blood, because it is able to relax more fully each time and to take in a correspondingly larger amount of blood. Under normal conditions, the output of the left ventricle equals that of the right. It might also be mentioned that these chambers are not emptied entirely with each systole, but that a small amount of "residual" blood is always caught in the recesses behind the different valve flaps.

While certain unavoidable difficulties in the methods make it impossible to present exact values regarding the cardiac output, it may be concluded that the average ventricular discharge per kilo of the body weight is somewhat greater in small animals than in large. In the dog, for example, values ranging between 50 and 90 c.c. have been obtained. The ventricular output in a man weighing 70 kilos, has been calculated at 87 grams with a cardiac frequency of 72 in a minute, but this value is probably somewhat too high. In accordance with the total quantity of blood present in the body, it has been calculated that 4.5 kilos of blood are propelled during 72 cardiac cycles and hence, 62.5 grams or about 60 c.c. of blood are ejected during each systole.

The Time Relation of the Cardiac Cycle.—Each cardiac cycle begins with the contraction of the auricles, these chambers being activated at practically the same time. It will be remembered, however, that the excitation-wave begins at the venous vestibule on the right side and hence, it has been possible to demonstrate that the left auricle lags behind the right by a fraction of a second. Fredericq,¹ who has determined this interval by exact graphic measurements, states that its duration is 0.01–0.03 sec.

The systole of the auricles is followed after an interval of 0.1 sec. by that of the ventricles. Obviously, this time is required for the passage of the wave of excitation through the bundle of His, but as the stimulus is distributed with equal rapidity to the different regions of the ventricles, these chambers are activated at practically the same time.² The essential fact to remember, therefore, is that the auricular cycle precedes the ventricular by about 0.1 sec. and hence, the antechambers complete their systole before the contraction of the main chambers actually begins.

If the cardiac rate is 70 in a minute, the systole of the auricles consumes 0.1–0.17 sec. and that of the ventricles 0.37 sec. Under the same conditions the diastole of the former occupies 0.76–0.69 sec., and that of the latter 0.48 sec. Thus, if the duration of each cardiac cycle is taken to be 0.8 sec., it may be said in a general way that the

¹ Arch. intern. de physiol., 1906, 57.

² Slight dissociations have been observed at times in disease, due probably to effects of blocking in the realm of the ventricular conducting paths.

period of contraction of the heart lasts 0.4 sec., and that of relaxation and rest 0.4 sec.¹ Under ordinary conditions, therefore, this organ rests as much as it works. Greater frequencies are attained at the expense of the pause until eventually even the amplitude of the contraction is lessened. The preceding discussion, however, will show that a frequency of 120–140 per minute may be obtained by simply dropping the pause.

E. THE PLAY OF THE VALVES

It must be clearly understood at this time that the movement of the valve flaps depends upon the differences in pressure to which their

FIG. 157.—THE INTRAVENTRICULAR (VP) PRESSURE IN RELATION WITH THE INTRA-AURICULAR PRESSURE (AP) AND THE HEART SOUNDS (S).

AB, auricular systole; *BD*, auricular diastole; *DA*, auricular pause; *BC*, ventricular systole; *CE*, ventricular diastole; *EB*, ventricular pause; 1, closure of auriculoventricular valve; 2, opening of semilunar valve; 3, closure of semilunar valve; 4, opening of auriculoventricular valve; *I*, *II* and *III*, first, second and third heart sounds.

upper and lower surfaces are exposed. To begin with, the blood flows into the diastolic auricles until it finally sets up a pressure which is just sufficient to push the auriculoventricular valve flaps downward. A part of the auricular contents are now enabled to escape into the relaxed ventricles. The mitral and tricuspid valves, therefore, open sometime before the onset of auricular systole, and permit the ventricular cavities to become partially filled even before the auricles actually begin their contraction (Fig. 157). Thus, the succeeding auricular systole (*AB*) merely serves the purpose of forcibly filling the ventricles until they are fully distended. Immediately following this phase, the auricles relax (*BD*), while the ventricles contract (*BC*) and develop a pressure far in excess of that prevailing in the ante-chambers. The auriculoventricular valves now close (1), and naturally, their closure

¹ More specific values are given in Tigerstedt's *Physiologie d. Kreislaufes*, Leipzig, 1893.

must be effected very shortly after the beginning of ventricular systole, *i.e.*, at the moment when the intraventricular pressure just barely rises above the intra-auricular. A fraction of a second later, the swiftly rising pressure opens the semilunar valves (2), and clearly, the outward displacement of these flaps must occur at the moment when the intraventricular pressure just barely overcomes the pressure prevailing in the arteries. As is indicated in the accompanying figure, the opening of the semilunar valves must take place late in systole at the beginning of the plateau. As soon as the ventricular musculature relaxes, the pressure in the ventricles falls below that prevailing in the arterial channels. In consequence of this reversion of the pressures, the semilunar valves are shut under the weight of the blood as it endeavors to seek a place of least resistance and return into the main

FIG. 158.—DIAGRAM TO ILLUSTRATE THE POSITION OF THE CARDIAC VALVES DURING (A) AURICULAR SYSTOLE AND (V) VENTRICULAR SYSTOLE.

Only one-half of the heart is represented.

chambers (3). The closure of the semilunar valves, therefore, is effected immediately after the beginning of ventricular diastole, *i.e.*, as soon as the intraventricular pressure falls below the arterial. Late in diastole, the auriculoventricular valves again open and permit the next pre-systolic filling of the ventricles (4).

It will be seen, therefore, that the ventricles are converted into completely closed cavities twice in the course of each cardiac cycle, but only for the briefest possible time (Fig. 160). This must be so, because the semilunar valves cannot open until the main chambers have been completely shut off against the auricles by the closure of the mitral and tricuspid valves (1 to 2). The semilunar valves close sometime before the mitral and tricuspid valves are opened by the inflowing auricular blood (3 to 4). It must also be evident that the ventricles do not eject their contents into the arteries as soon as their systolic movement begins, but only subsequent to the moment when the intraventricular pressure exceeds that prevailing in the arterial trunks. The *discharging period* of these cavities, therefore, begins with the opening of the semi-

lunar valves and continues throughout the plateau (2 to 3). It ceases with the beginning of diastole, *i.e.*, as soon as the semilunar valves are closed by the high outside pressure. The early phase of systole during

FIG. 159.—SCHEMA TO SHOW ARRANGEMENT OF APPARATUS FOR DEMONSTRATING THE ACTION OF THE HEART VALVES.

A, reservoir for water; H, ox heart; B and C, windows inserted in the orifices of the pulmonary vein and aorta overlying the mitral and aortic valves; E, electric battery and light used to illuminate ventricular cavity; P, pump by means of which water is made to circulate and to close and open the valves.

which the ventricles simply contract upon their contents without actually ejecting the blood, is known as the “*setting period.*” Its dura-

FIG. 160.—SYNCHRONOUS RECORD OF THE INTRAVENTRICULAR PRESSURE (V), AND THE AORTIC PRESSURE (A)

S, the time record, each vibration = $\frac{1}{100}$ sec.; 0-5, corresponding ordinates in the two curves; 1 marks the opening of the semilunar valves; 3 (or shortly after) marks the closure of these valves and the beginning of diastole. (Harthle.)

tion is 0.02-0.04 sec. The *period of filling* of the ventricles commences with the opening of the auriculoventricular valves late during diastole and ceases with the beginning of the next auricular systole.

SECTION VIII

THE NERVOUS REGULATION OF THE HEART

CHAPTER XXVII

CARDIAC INHIBITION AND ACCELERATION

General Discussion.—It is a well-known physiological fact that the heart continues its activity not only after it has been isolated from the central nervous system by severing all its nervous connections, but also after it has been removed from the body. The excised organ of the lower forms, for example, will beat rhythmically for hours and even for days, provided, of course, that it is kept under proper conditions of temperature and moisture, and is supplied with a nutritive fluid of some kind. Results very similar to these may be obtained with the hearts of mammals, but as the activity of these organs is more closely dependent upon an adequate blood supply, they must be handled with much greater care. These experiments show very clearly that the contractions of the heart as such are not due to discharges from the central nervous system, although it must be admitted that a proper correlation of the function of this organ with that of other structures cannot be achieved unless its nervous connections with central parts have been preserved. It may be concluded, therefore, that the inherent power of the heart to contract is regulated under normal conditions by a nervous mechanism consisting of a center and efferent and afferent paths.

The Cardiac Center.—The nerve cells controlling the action of the heart, are situated in the gray matter of the medulla oblongata below the floor of the fourth ventricle and near the tip of the calamus scriptorius. This center, therefore, lies in the vicinity of the respiratory and vasomotor centers, but its exact location has not been definitely ascertained as yet. Suffice to say that this part of the central nervous

FIG. 161.—THE NERVOUS INNervation OF THE HEART.

CC, cardiac center; M, motor path consisting of cardio-inhibitor and cardio-accelerator fibers; E, effector, heart muscle; S, sensory path conveying impulses from different receptors (R), such as the retina, cutaneous sense-organs, etc.

system gives lodgment to a certain number of ganglion cells which give origin to the efferent cardiac fibers and serve as the terminal station for a number of afferent channels. It should also be mentioned that this center, as mapped out at the present time, possesses solely an inhibitor function. The co-existence in this region of an accelerator zone has not been established as yet but may be surmised upon the basis of indirect evidence. Since the nervous system is bilaterally arranged, there are of course two centers and two sets of fibers, one on each side of the median line of the body.

The Efferent or Cardiomotor Fibers.—These fibers are inhibitor and accelerator in their function. The inhibitors reach the heart by way of the vagus or pneumogastric system, and the latter by way of the cervical spinal cord and the thoracic sympathetic ganglia. Both actions, of course, are autonomic, *i.e.*, they are not under the direct control of the will.

The inhibitor fibers were discovered in 1845 by E. H. and E. Weber.¹ They are found in all vertebrates as well as in many invertebrates. In man, their presence has been fully established by Czermak,² Thanhoffer,³ and others. They arise in the nucleus of the vagus and follow the highway of this nerve to the heart. Moreover, while they pursue a perfectly independent course in some animals, such as the woodchuck (Simpson), they are most frequently combined with other fibers having an entirely different function. The cardiac branches of the vagus are commonly designated as the superior and inferior cardiac rami. The former arise from the cervical portion of the vagus somewhere between the superior and inferior laryngeal nerves, while the latter take their origin from the thoracic portion of this nerve as well as from the nervus recurrens directly. Having attained the region of the heart, they enter into relation with certain fibers of the thoracic sympathetic system (nervus accelerans) to form the plexus cardiacus which envelops the ascending portion and arch of the aorta. From here they are distributed to the nerve centers (Remak's) situated in the domain of the heart, as well as to the more distant cardiac musculature. Those fibers which connect the nucleus of the vagus with the intracardiac centers, constitute the preganglionic path; and those which unite the intracardiac plexus with the muscle substance, the postganglionic path.

Division of the vagi nerves has been practised several times since the day of Rufus of Epheus and Salenus. Willis and Lower observed toward the end of the seventeenth century that this procedure leads to a more violent pulsation of the heart, this result being attributed to a weakness of the heart. In 1838, Volkmann noted that an inhibitor effect upon the heart may be produced by stimulation of the vagus nerve with a constant current. Budge employed an electromagnetic rotation apparatus with similar results, but failed to give an adequate explanation of this phenomenon.

¹ Handb. der Physiol., iii, 1846.

² Prager Vierteljahrschr., 1868, 100.

³ Centralbl. für die med. Wissensch., 1875.

The existence of **accelerator fibers** has been established experimentally in rabbits by von Bezold¹ whose results have been substantiated for warm-blooded animals by M. and E. Cyon,² and for cold-blooded animals by Schmiedeberg.³ Although it cannot be definitely stated that these fibers arise in or near the cardio-inhibitor center of the medulla, it may justly be assumed that they possess a central origin

FIG. 162.—SCHEMA ILLUSTRATING THE DISTRIBUTION OF THE CARDIAC NERVES.

MO, medulla oblongata; CC, cardiac center (inhibitor area); X, nucleus of vagus nerve, red indicating the course of the inhibitor fibers; SCR, superior cardiac ramus; JCR, inferior cardiac ramus; V, vagus; SL, superior laryngeus; JL, inferior laryngeus; PC, plexus cardiacus, and preganglionic path; SC, spinal cord, the accelerator fibers are indicated in blue, II, III, and IV roots of corresponding thoracic spinal nerves; S, sympathetic ganglion along spinal cord; SG, stellate ganglion; AV, annulus of Vieussens; JC, inferior cervical ganglion to plexus cardiacus upon arch of aorta.

and are at least intimately connected with this area. They become clearly recognizable peripherally in the anterior roots of the second, third and fourth thoracic spinal nerves; in fact, in certain animals also in the lower cervical and first and fifth thoracic nerves. The nerve cells from which they arise are situated in the intermedio-lateral tract of the spinal cord. For this reason, they may be regarded as forming

¹ Untersuch. über die Innervation des Herzens, ii, 1863.

² Centralbl. für die med. Wissensch., 1866.

³ Ber. der sächs. Gesellsch. der Wissensch., 1870.

a spinal cardio-accelerator center. It may be surmised that this spinal center is controlled in turn by a higher center located in the medulla oblongata near the cardio-inhibitor center. These spinal accelerator fibers finally reach the ganglion stellatum by way of the white rami communicantes (dog) and pass by way of the annulus of Vieussens to the inferior cervical ganglion. Their terminals are to be found in these ganglia, where they form synapses with other cells. Fresh relays of non-medullated fibers continue onward through the cardiac plexus to the musculature of the heart. The latter connection seems to be effected without the intervention of intracardiac nerve cells, while the

FIG. 163.—SKETCH TO SHOW THE ACCELERATOR (AND AUGMENTOR) BRANCHES FROM THE STELLATE GANGLION (IN THE CAT, LEFT SIDE).

1, the ventral branch of the annulus (ansa subclavia); 2, small branch not constantly present; 3, Boehm's accelerator nerve (N. cardiacus and ganglion stellatum). (Howell.)

inhibitor fibers, as has been mentioned above, are intimately associated with Remak's as well as with other intrinsic ganglia of the heart. The accelerator fibers may be stimulated at almost any point of their course. Very favorable conditions prevail in the cat in which animal a distinct nervus accelerans extends between the stellate ganglion and the cardiac plexus.

The Character of the Inhibition.—

If a moderate mechanical, chemical, or electrical stimulus is applied to the intact vagus, the normal rhythm of the heart soon gives way to a much slower one. The strength of the stimulus may then be increased until this organ becomes more and more diastolic and finally ceases its activity altogether. A functional diminution of this kind, or *inhibition*, as it is commonly called, may be obtained by applying the stimulus to any point of this nerve, in fact, even to its nucleus in the medulla. Under ordinary conditions, however, its cervical portion is selected for the

excitation, because it is more accessible than its cranial or thoracic portions. It should also be remembered that the inhibitor mechanism is not equally receptive or sensitive in all animals, and secondly, that the inhibitor power of the right and left vagi differs somewhat even in the same animal. Thus, it is rather difficult to cause a complete arrest of the heart of the cat, while it is comparatively simple to attain this result in the dog. Quite similarly, it is often impossible to cause an inhibition with the aid of one vagus, while the stimulation of the opposite nerve gives an almost immediate maximal effect. In frogs, turtles, and snakes, the right nerve is generally the stronger, while in those mammals which are usually used for

purposes of experimentation, either the right or the left nerve may be the more effective. As the inhibitor impulses pass from the vagus center to the periphery, *i.e.*, in an efferent direction, it may readily be gathered that the inhibition may also be obtained by stimulating solely the distal end of the divided vagus. In the frog, turtle and allied animals, it is also possible to arrest the heart by applying the electrodes directly to its sino-auricular region, because this particular area gives lodgment to a plexus which possesses an inhibitor function and may therefore represent the principal peripheral relay station of the vagus.

The inhibition of the heart is characterized by a gradual preponderance of its diastolic period. Its systolic movement is hindered more and more until its musculature temporarily enters a state of complete relaxation. The organ as a whole becomes greatly distended

FIG. 164.—RECORD OF THE CONTRACTIONS OF THE FROG'S HEART DURING STIMULATION OF THE VAGUS NERVE.

The time is given in seconds, the stimulation is indicated by the signal.

with blood and exhibits a pronounced venous appearance. The inhibition appears as a rule after a brief latent period and continues for a few moments after the cessation of the excitation. Furthermore, while the principal effect of the stimulation consists in a diminution of the frequency of the heart, this inhibition is frequently associated with a reduction in the amplitude of the individual contractions. Weak stimuli, for example, are prone to affect solely the rate and to give merely a partial cessation of the contractions, while stronger stimuli diminish the height as well as the frequency of the contractions until a complete stoppage has been obtained. The strength of the stimulus, however, is not the only factor determining these effects; in fact, we shall see later on that they find their origin in certain functional peculiarities of the inhibitor mechanism.

The inhibited heart resumes its activity by giving a contraction which is either smaller or much larger than normal. In either case, the beats regain their former amplitude gradually within a few moments. It is to be noted, however, that the heart cannot be kept in the inhibited state for any length of time, because it resumes

its beat automatically whenever the stimulation is unduly prolonged. It seems, therefore, that the excitation eventually induces a fatigue of the inhibitor mechanism which permits the accelerator influences to gain the upper hand. This "escape" of the organ from the power of the vagus is generally confined to its ventricular portion, the auricles remaining in the state of diastole. No definite statement can be made regarding the length of time during which it is possible to maintain the inhibition. In warm-blooded animals, the "inner stimulus" most generally makes itself felt in the course of a few seconds, while in

cold-blooded animals it does not exert itself until after several minutes. To begin with, the heart gives a few isolated beats, and then gradually more until the normal rhythm has again been established.

The inhibition is frequently followed by an augmentor effect which is characterized by an increased frequency, or strength of contraction, or both. This *secondary augmentation* is especially well shown in the frog, in which animal the vagal and sympathetic fibers are united into a common nerve at some distance from the heart. For this reason, the inhibitor as well as the augmentor fibers are affected whenever the trunk of the vagus is stimulated. Their combined excitation, however, gives rise to an inhibition. If it is desired to stimulate the inhibitor fibers separately, the electrodes must be applied to

FIG. 165.—COURSE OF VAGUS NERVE IN FROG. (Stirling.)

SM, submental; LU, lung; V, vagus; GP, glosso-pharyngeal; HS, hypoglossal; L, laryngeal; PH, SH, GH, OH, petro-, sterno-, genio-, and omohyoid; HG, hypoglossus; H, heart; BR, brachial plexus.

them as they emerge from the vagal foramen and before they have joined the sympathetic fibers. In explaining the fact that the excitation of the combined vagosympathetic fibers always leads to an inhibition, it must be remembered that the augmentation requires stronger stimuli, possibly because the inhibitor mechanism is more sensitive, or because the latent period of the augmentors is longer than that of the inhibitors. Moreover, even if these impulses are generated at precisely the same moment, as they probably are when the vagus itself is stimulated, they cannot be pitted against one another, because the augmentor influence cannot be made to antagonize the inhibitor. Neither can the latter be made to counteract the former. It seems, therefore, that each impulse, when once started, must run its course until the reaction to which it contributes has been fully completed. Thus, as the inhibitor effect is produced

more easily, the augmentor effect cannot develop until the inhibition has been brought to a close, or has lost its initial power. In mammals, such as the dog, cat, and rabbit, the effects of the stimulation of the vagus are very similar to those noted in the frog and turtle, with this exception, however, that the secondary augmentation is less pronounced. It also seems that in these animals the augmentor and the inhibitor fibers antagonize one another in a direct manner, because the excitation of the former tends to lessen the action of the latter.

The Nature of the Inhibition.—Before entering upon a discussion of this topic, brief reference should be made to the question of whether the vagal impulses are distributed solely to the auricles or to the ventricles, or to both parts. Thus, it may be held, on the one hand, that their influence is apportioned equally to all parts of the organ and, on the other, that it is distributed solely to the auricle and particularly to the area of the “pace-maker.” In the first instance, therefore, the cardiac musculature would be affected directly and, in the second, solely through the intervention of the sino-auricular node. The latter view necessitates the assumption that the ventricle is rendered inactive on account of the failure of the “pace-maker” to discharge those waves of excitation which ordinarily give rise to its activity. Gaskell has submitted certain evidence to show that in the terrapin the inhibitor impulses are received by the auricle, and that the ventricle ceases to beat because no stimuli are apportioned to it by the “pace-maker.” In the frog, on the other hand, the ventricle is under the direct control of the vagus, quite independently of the auricles. A similar relationship seems to exist in the mammals, the vagus fibers being distributed to the auricles as well as to the ventricles.¹ This is shown by the fact that the contractions of the auricular and ventricular musculature may be dissociated and even reversed.

The vagal impulses produce their characteristic effect either by causing the musculature to relax, or by diminishing the power of conduction of the bundle of His and its ramifications. On the whole, however, the experimental evidence favors the view that the vagus exerts its action primarily through the auricles and the “pace-maker” and that its direct action upon the ventricles is slight and is made use of only under singular circumstances. Engelman² classifies the cardiomotor impulses as follows:

- (a) Chronotropic, affecting the rate of the contractions.
- (b) Inotropic, affecting the force of the contractions.
- (c) Bathmotropic, affecting the irritability of the muscular tissue, and
- (d) Dromotropic, affecting the conductivity of the tissue.

Every one of these influences is said to be either of a positive or negative kind. The former result in consequence of the excitation of the accelerator, and the latter in consequence of the stimulation of

¹ Tigerstedt (*Lehrb. der Physiol. des Kreisl.*, Leipzig, 1893), Frank (*Arch. der Physiol.*, 1891), and McWilliams (*Jour. of Physiol.*, ix, 1888).

² *Arch. für Physiol.*, 1900 and 1902.

the inhibitor mechanism. In addition, these reactions are believed to be brought about with the aid of four different sets of nerve fibers. In the light of the preceding discussion, however, it would seem that these different peculiarities of the heart beat should rather be ascribed to certain differences in the manner of distribution of these impulses to the cardiac musculature.

Another question to be considered at this time, pertains to the *specificity of the vagus nerve*. It has been stated above that the cardio-inhibitor effect can only be induced with the help of this particular nerve, because it forms the sole connection between the central nervous system and the inhibitor end-organs in the heart. It is, however, a well-known physiological fact that the character of a reaction does not depend upon the nerve as such, but upon the structural and functional peculiarities of the end-organ with which it is connected. The vagus nerve does not form an exception to this rule, and hence, it must be concluded that its function is to conduct impulses, while the inhibition depends upon certain peculiarities of the cardiac effectors. For this reason, the cause of the inhibition of the heart must be sought at the periphery, namely, in certain physico-chemical alterations in the vagal terminals and neighboring muscle cells. The specificity of the vagus, therefore, is, so to speak, "accidental."

FIG. 166.—SCHEMA TO ILLUSTRATE THE ACTION OF NICOTIN.

V, vagus, preganglionic path; SAP, sino-auricular plexus; P, postganglionic path; N, nicotin breaks connection between vagal terminals and postganglionic cell.

In substantiation of this statement, it might be mentioned that it is possible to establish a functional union between the central end of the divided fifth cervical nerve and the distal stump of the vagus. Peculiarly enough, the excitation of this formerly musculo-motor nerve invariably leads to an inhibition of the heart. In a similar way, this organ could be inhibited with the help of any other efferent nerve, but only in case a crossing of its fibers with those of the vagus is an experimental possibility.

The preceding statements regarding the specificity of the vagus find substantiation in the changes which the inhibitor reaction suffers in consequence of the administration of certain drugs, such as *nicotin*, *atropin* and *muscarin*. To illustrate, if the heart of a frog or turtle is moistened with a weak solution of nicotin, the stimulation of the vagus (V) becomes ineffective as soon as this agent has had sufficient time to penetrate the cardiac tissues. At this time, however, the excitation of the plexus at the sino-auricular junction (SAP) of the heart still gives rise to an inhibition. Nicotin is a cell poison; its action being centered upon the dendritic filaments of the neurone. It may be concluded, therefore, that it breaks the connection between

the terminals of the vagus and the cells of the intracardiac plexus (Remak's) which innervate the peripheral inhibitor mechanism. Consequently, the stimulation of the preganglionic path, constituted by the vagus nerve, must remain without effect, while the excitation of the postganglionic path, formed by the cells of the aforesaid ganglion and their distal axons, must give rise to an inhibition.

If atropin is applied to the heart, or is administered in a general way, negative results are obtained on excitation of the vagus (V), as well as on excitation of the sino-auricular plexus (SAP). By inference, therefore, it may be concluded that this alkaloid produces a break in the conducting path peripherally to this intracardiac ganglion, so that the cardio-inhibitor impulses are no longer able to reach the end-

FIG. 167.

FIG. 167.—SCHEMA TO ILLUSTRATE THE ACTION OF ATROPIN.

V, vagus, preganglionic path; SAP, sino-auricular plexus; P, postganglionic path; A, atropin breaks the connection between the postganglionic path and the cardiac muscle.

FIG. 168.

FIG. 168.—SCHEMA TO ILLUSTRATE THE ACTION OF MUSCARIN.

V, vagus, preganglionic path; SAP, sino-auricular plexus; P, postganglionic path; M, muscarin breaks the connection at the neural junction or paralyzes the musculature itself.

organ. The cardio-accelerator influences, on the other hand, are not blocked and hence, we observe at this time a marked increase in the frequency of the heart. Atropin is a fiber poison and paralyzes the postganglionic terminals. In time to come, this agent is oxidized or is excreted in its original form. As its action wears off, conduction is gradually restored so that the stimulations of the vagus and of the intracardiac ganglion again become effective.

Pilocarpin and muscarin, whether applied directly to the heart or administered internally, diminish the frequency and amplitude of the contractions and finally produce a diastolic stoppage. Two views are held regarding the action of these drugs. It is believed, on the one hand, that they paralyze the cardiac muscle tissue directly, and, on the other, that they increase the irritability of the nerve-tissue in such a degree that the inhibitor mechanism is under constant

excitation. The second explanation, proposing that the inhibition is due to a stimulation of this mechanism, has met with greater favor, probably because it can be brought into closer relation with the view regarding the action of atropin, which agent, in contradistinction to muscarin, depresses the inhibitor mechanism by lessening the irritability of the postganglionic fibers and their ramifications. This explanation is made use of in accounting for the fact that the inhibition established by pilocarpin or muscarin may be removed later on by the administration of atropin. It must be evident, therefore, that this agent possesses the power of neutralizing the action of muscarin so that the normal rhythm may again be restored. In accordance with this view, it is believed that the antagonistic action of the drugs just mentioned depends upon the fact that the atropin causes the irritability of the inhibitor end-organs to be gradually diminished.

It must be acknowledged, however, that the first view, expressing the idea that muscarin and atropin affect the cardiac musculature directly, is not without foundation. Thus, it has been shown that these drugs give rise to the aforesaid functional changes even in the hearts of mammalian embryos at a time when nervous structures have not made their appearance as yet, or at least, long before the nervous connections have been fully formed. Besides, it has been established that muscarin does not affect the hearts of many vertebrates.¹ This evidence, however, may be met with the objection that the properties of the fully developed organ cannot justly be compared with those of the embryonic organ, and secondly, that the action of these alkaloids need not be the same in all animals.

Some interesting data regarding the distribution of the cardiac impulses may also be gathered from a number of phenomena which have been described by Stannius. If a thread is tied rather loosely around the heart of a frog or turtle at the sino-auricular junction, the sinus continues to beat rhythmically, while the remaining portion of the heart ceases its activity. This result is explicable upon the basis that the wave of excitation is blocked at the seat of the ligature, but it is also possible that the latter serves as a mechanical stimulus to the inhibitor elements situated in the domain of the sino-auricular groove (Remak's ganglion). Curiously enough, if a second ligature is now applied to the heart at the auriculoventricular junction, all three parts of the organ again contract, but their beats are no longer coördinated. This phenomenon is difficult to explain unless it is assumed that the second ligature stimulates certain accelerator elements situated in the region of the auriculoventricular groove (Bidder's ganglion). This favors the production of an independent rhythm in the auricles and ventricle.

The Cause of the Inhibition.—It need scarcely be mentioned that the activation of a tissue is always associated with the destruction of

¹ For a more detailed discussion, see Cushing's *Pharmacology and Therapeutics*, London, 1915.

certain of its constituents. This phase of disintegration, however, must always be followed by a period during which the material lost is again replenished. In other words, catabolism must be succeeded by anabolism, otherwise the destruction of the living material becomes complete. In accordance with Claude Bernard, the state of inhibition is merely a prolonged period of rest, made necessary by the fact that cardiac muscle, when stimulated, requires an unusually long time for its processes of restitution. Hering and Gaskell have gone one step farther and have suggested that the vagus possesses a true constructive function in that it favors the occurrence of metabolic changes. Thus it is held that the excitation of the vagus not only promotes the continuance of that intensity of anabolism which is usual during diastole, but actually augments the processes of breaking down and building up. These data have been made use of by Gaskell¹ in the formation of the so-called trophic theory of inhibition. The contention is that the inhibitor fibers which, as has been shown, are generally included in the vagus nerve, may be looked upon as constituting an anabolic nerve of the heart and must, therefore, be of greatest importance to the nutritive processes going on in this organ. In accordance with this view, the after-effects of their excitation must be very beneficial, because a greater formation of contractile material must result therefrom which in turn insures an increased functional capacity of the musculature. In order to strengthen this theory, Gaskell has attempted to prove that these trophic alterations are associated with definite electrical changes. It has been known for a long time that the active part of a tissue is electronegative to its resting part. Quite similarly, it may be assumed, in accordance with the preceding exposition, that the inhibited area of the heart is electropositive to the non-inhibited. In order to prove this point, the auricles of a turtle's heart were rendered inactive by separating them from the sinus venosus. One of the poles of a galvanometer was then connected with the base of the auricles, while the other was permitted to rest upon the apical region which, however, had previously been injured by heat. To begin with, therefore, the aforesaid instrument registered a demarcation-current, the direction of which indicated an electronegativity at the injured apex. If the auricles were now made to contract, this "current of injury," immediately gave way to a "current of action." Moreover, if the vagus nerve was stimulated at this time, a positive variation resulted, indicating the production of an electrical change opposite in potential to that encountered during the contraction of these parts.

Another theory which is based upon the well-known fact that potassium salts promote the relaxation of the cardiac musculature, has been proposed by Howell and Duke.² It is held by these authors that the stoppage of the heart is dependent upon the liberation of

¹ Jour. of Physiol., vii, 1886, 451.

² Am. Jour. of Physiol., xxi, 1908.

potassium which, on being set free, temporarily inhibits the systolic processes. Several facts might be cited in support of this view. Thus it has been shown that this salt, when added in certain amounts to the perfusion fluid, gives rise to a diastolic arrest of the heart which closely resembles that resulting from the excitation of the vagus. Under these conditions, the inhibitor power of the vagus may be restored at any time by simply removing the excess of the potassium. Use is also made of the observation that this salt exists in large quantities in cardiac muscle and that a heart gives off unusual amounts of diffusible potassium whenever it is inhibited with the aid of the vagus. In accordance with the aforesaid theory, it is held that the vagus impulses incite a cleavage of some kind of the combined tissue-potassium so that some of it is set free in a soluble form. The subsequent interaction between the potassium thus rendered available and the cells of the heart, occurs chiefly in that region in which the beat originates. The latter amplification of this theory serves to explain the fact that an inhibited heart retains its irritability toward direct stimulation. Hemmeter¹ has attempted to test this theory experimentally by analysis of the ash of the blood contained in inhibited hearts, as well as by arresting the activity of a normally beating heart by supplying it directly with the blood of an inhibited organ. The results of these experiments, however, have failed to substantiate the preceding contentions so that they cannot be regarded as having been removed from the realm of a mere hypothesis.

The Result of the Inhibition.—It may be inferred from the above discussion that the inhibitor mechanism does not cease its activity at any time. Impulses are discharged by the cardiac center with rhythmic regularity. They are then conducted to the heart, where they tend to hold this organ in check. In this way, the automatic activity of this organ is subjected to a constant restraint with the result that a normal frequency and amplitude of contraction is obtained. But whenever this check is removed, the accelerator influences gain the upper hand and finally produce an augmentor effect. In an experimental way these inhibitor impulses may be prevented from reaching the periphery by simply dividing the conducting path (Fig. 169). Obviously, therefore, the section of the vagi nerves must lead to an increase in the rate of the heart, and naturally, this increase must become the more evident, the less the original frequency of contraction.

These constant discharges from the inhibitor center may also be blocked by cooling the vagi nerves at any point of their course, or by moistening them with an agent which diminishes their conductivity, for example, with magnesium sulphate. In this connection it should be emphasized again that the inhibitor power of these nerves is not equal and hence, their division is usually followed by varying degrees of acceleration. Thus, it may happen that the section of only one of the vagi nerves produces scarcely any acceleration, while the division

¹ Biochem. Zeitschr., 1914, 63.

of the other nerve alone suffices to give a maximal effect. Either the right or the left nerve may be the more powerful. It need scarcely be mentioned that these inhibitor reactions may also be incited by the stimulation of the distal end of the divided vagus, the electrodes being applied either to the right or to the left nerve. In some animals (cat) it is also possible to produce a moderate inhibition by stimulating the central stump of either vagus, provided, of course, that the opposite nerve has been left intact. This effect is easily explained, because

FIG. 169.—To SHOW THE EFFECT OF SECTION OF THE TWO VAGI IN THE DOG UPON THE RATE OF HEART BEAT AND THE BLOOD-PRESSURE.

1, Marks the section of the vagus on the right side; 2, section of the second vagus. The numerals on the vertical mark the blood-pressures; the numerals on the blood-pressure record give the rate of the heart beats. (Dawson.)

these nerves also conduct impulses from the heart to the center, where they affect the cardiomotor mechanism in a reflex way. In most cases, these afferent stimuli give rise to an inhibition, but it also happens at times that they incite a slight augmentation. This result is usually observed in dogs.

If the blood pressure is registered during these stimulations of the vagus nerve, it can readily be established that the inhibition of the heart is associated with a fall in the arterial and a rise in the venous

pressure.¹ These changes prove very clearly that the stoppage of this organ is followed by a gradual transfer of the arterial blood into the central veins, right auricle and ventricle. We obtain, therefore, a condition very similar to that found at death, when the recoiling arteries force the blood into the venous collecting channels. The arterial blood pressure rises again with the return of the cardiac contractions. The venous pressure drops proportionately. It is to be noted, however, that the systoles occurring directly after the inhibition cause more decided changes than those taking place later on, because the gradual refilling of the arterial system and returning tension must necessarily lead to a corresponding diminution of the systolic-diastolic difference in pressure. When the cardiac output has again become normal, the pressures assume their former level. In most cases,

FIG. 170.—RECORD OF CAROTID BLOOD-PRESSURE.

S, stimulation of left vagus nerve. The fall in pressure is followed by compensatory changes before the normal pressure is again established.

however, the arterial pressure does not become constant until it has first risen somewhat above its normal value. In fact, this initial rise above normal is frequently followed by a fall below normal. These oscillations, occurring in the wake of the inhibition, are dependent upon the attempt on the part of the arterial system to compensate for the loss in pressure. To begin with, the arteries constrict more and more, as the blood leaves them to enter the veins. In this condition, they remain until the first ventricular discharge subsequent to the inhibition again distends them. The resistance thus placed in the path of the successive cardiac outputs tends to raise the pressure rather abruptly so that its normal value is temporarily exceeded. At this very moment the vasoconstriction gives way to a vasodilatation with

¹ Burton-Opitz, *Am. Jour. of Physiol.*, ix, 1903, 198.

the result that the pressure now falls somewhat below its normal level. Subsequent to this point normal conditions are again established.

As might be expected, these compensatory changes are not always of the same intensity, because the irritability of the vasomotor mechanism differs in the same degree as that of the entire nervous system. It is obvious, however, that a close reflex correlation exists between the cardiac and vasomotor centers, so that a reduction in the ventricular output may be compensated for immediately by a constriction of the blood-vessels. This is of greatest importance, because the functions of the different colonies of cells in our body must necessarily cease, if the pressure under which they obtain their nutritive material falls below a certain minimal value. For this reason, even a relatively brief inhibition of the heart must be associated with a general depression of function which makes itself felt most strikingly by a loss of our psychic activities. If continued for an undue length of time, the inhibition must necessarily be followed by certain disturbances of function which are not so easily compensated for and remedied. The "escape of inhibition" may be said to constitute a safety device of the body to prevent fatal consequences from this source.

The Character and Nature of the Acceleration.—The action of the accelerator fibers may be tested experimentally in mammals as well as in lower forms. In the former, these fibers may be isolated distally to the thoracic sympathetic ganglia, while in the frog and allied animals, they may be rendered accessible directly beside the vertebral column. As is indicated in Fig. 171, the latter eventually unite with those of the vagus and finally terminate in the heart. The cardiomotor fibers, therefore, may be reached in this animal in three different places. Their stimulation at *A*, where the vagus alone is affected, results in an inhibition, while the stimulation of the sympathetic chain at *B* gives acceleration. For reasons discussed previously, the excitation of the vagosympathetic at *C* is followed by an inhibition.

The accelerators produce their effect after a considerable latent period, but when once established, the acceleration continues as a rule for some moments after the cessation of the excitation. Ten or twenty seconds frequently elapse before a marked increase in the cardiac rhythm is observed, while, in the case of the vagus, the latent

FIG. 171.—SCHEMA TO SHOW THE COURSE OF THE CARDIAC NERVES IN THE FROG.

A, vagal fibers are still separate; *B*, sympathetic fibers are still separate; *C*, both types of fibers have combined to form the vagosympathetic nerve. 2, Remak's ganglion; *B*, Bidder's ganglion.

period is less than one second. Clearly, therefore, the sympathetic or accelerator fibers react more sluggishly but are less easily fatigued than the inhibitor. The effect of their excitation consists either in an acceleration or in an augmentation; in fact, in some cases both changes are obtained simultaneously, the contractions becoming more frequent as well as more forcible. In explaining this result, it is generally stated that the accelerator mechanism is adjusted in such a way that it may give rise to two reactions, namely, an increase in the frequency, and an augmentation in the amplitude of the individual beats. In analogy with this functional dissociation, it is also held that the inhibitor mechanism is adjusted in such a way that the inhibition may be accomplished either by lessening the frequency, or by decreasing the amplitude of the cardiac contractions.¹

While the experimental evidence is not very conclusive, it has been suggested that the accelerator center discharges its impulses in rhythmic succession, thereby establishing the so-called accelerator tonus in antagonism to the inhibitor tonus. The removal of the former influence, therefore, places the inhibitor discharges in complete control. A slowing of the heart is the result of this disturbance of the cardio-motor equilibrium. This end can be attained either by dividing the accelerator fibers themselves, or by removing the intrathoracic ganglia. Upon this basis cardio-acceleration may be explained by assuming that the inhibitor tonus is temporarily diminished.²

The increase in the rate of the heart is made possible by a shortening of each cardiac cycle, the duration of the diastolic period being reduced first of all. It may be stated in general that the simultaneous occurrence of accelerator and augmentor influences gives rise to a higher blood pressure and more effective circulatory conditions than one of these reactions alone could possibly produce. Thus, a simple acceleration may fail absolutely in improving hemodynamical conditions for the obvious reason that a greater number of ventricular discharges alone does not suffice to increase the cardiac output per unit of time, because the filling power or power of relaxation of the heart may have been diminished in a measure to offset the increased rate.

The Afferent or Cardiosensory Fibers.—These fibers are divided into two groups, namely, those which bring the cardiac center into relation with the various regions of the body, and those which connect it with the heart and neighboring pericardial and mediastinal membranes. The first group embraces a large number of nerves, because practically any one of the afferent paths in our body may at times convey impulses to central parts which here affect the activity of the heart in a reflex manner. The second group includes the ordinary sensory nerves

¹ Bayliss and Starling, *Jour. of Physiol.*, xiii, 1892, 407.

² Several cases have been recorded of persons who could voluntarily increase their heart rate (West and Savage, *Arch. Int. Med.*, 1918, 298). The acceleration was accompanied by an augmentation of the respiratory movements and a dilatation of the pupils.

of the cardiac region and also a number of inherent fibers which are commonly designated as the *depressor nerve*. The latter arise in the plexus cardiacus and use the highway of the vagus nerve in reaching the medulla oblongata. In the rabbit, they pursue a separate course, entering the vagus by two rami, one of which unites with the superior laryngeal nerve.

If we confine ourselves for the present to the general type of cardio-afferent nerves, it will be noted that the cardiac center is constantly played upon by various impulses which reach it through the different afferent channels of our body and are then transferred either to the cardio-accelerator or cardio-inhibitor mechanism. Thus, while the heart is capable of contracting independently of its center as well as of the rest of the body, its activity is regulated under normal conditions in such a manner that it fully conforms to the functions of other organs and tissues. Naturally, this correlation can only be attained with the aid of diverse afferent impulses which are poured into the cardiac center at different times and vary its automatic discharges so as to give the results previously described. We are dealing, therefore, at this time with typical cardiac reflexes.

This statement raises the question of whether the automatic activity of the cardiac center is maintained by stimuli which are generated by its constituents, or whether these stimuli are conveyed to it from other parts of the body. Although little is known regarding the peculiar processes occurring in ganglion cells, it may be assumed that nervous impulses result in consequence of certain physicochemical alterations within the cell. It is a well-known fact, however, that intracellular reactions of this kind cannot continue for an indefinite period of time unless extraneous influences are at hand to cause these internal changes to be repeated. Cellular retrogression and disintegration always follow in the wake of loss of stimulation. The constituents of the cardiac center do not form an exception to this rule, because the permanent removal of these afferent stimuli soon reduces them to a state of inactivity. For this reason, it may justly be assumed that the normal tone of these ganglion cells is largely dependent upon reflex stimulation.

To summarize, the activity of the heart is normally regulated by the cardiac center, the discharges of which are constantly varied in

FIG. 172 — DIAGRAM TO SHOW THE COURSE OF THE DEPRESSOR NERVE IN THE RABBIT.

L, larynx; T, thyroid gland; J, int. jugular vein; C, carotid artery; S, sympathetic nerve extending between the superior and inferior cervical ganglia; V, vagus nerve; SL, sup. laryngeal nerve; D, depressor nerve, entering the vagus by two branches. The vagus is pulled over, permitting the sympathetic to appear next to the carotid artery.

accordance with the character of the afferent impulses received by it. Two views are held regarding the nature of this control. In the presence of an accelerator and inhibitor mechanism, it is believed that the cardiac musculature is constantly under the influence of two types of impulses which are antagonistic to one another in so far as the first tends to increase, and the second to decrease the contractions. Consequently, the cardiac frequency must be regarded as the product of the interaction between these two factors. The afferent impressions received by the center shift the balance either in the direction of acceleration or inhibition. They accomplish this end by causing a greater number of impulses of either the former or latter kind to be generated and to be conducted to the heart. In accordance with the second view, it is held that the activity of the heart can only be increased by a depression of the inhibitor mechanism.¹ Thus, it is assumed that the afferent impulses, on reaching the cardiac center, lessen the restraint under which the heart is constantly held, and thereby permit the accelerator influences to gain full power. In the absence of definite facts, it is somewhat difficult to decide which of these two processes is normally at work. It would seem, however, that the frequency of the heart is regulated under normal conditions solely by the inhibitor center, slight changes in the rate of contraction being effected by alterations in the tonus of the latter. Greater variations as well as augmentor effects, however, necessitate an active opposition to the inhibitor influences by the accelerator center. For this reason, the latter may really be regarded as an aid to the former; its active participation being required whenever especially marked results are to be obtained.

It has been stated above that almost all sensory nerves convey afferent impulses to the cardiac center and hence, practically all receptors are in communication with the cardiomotor mechanism. Chief among these are the retina, the organ of Corti, the semicircular canals, the olfactory cells, the taste-buds, as well as the cutaneous and visceral end-organs for touch, pain, and temperature. The impressions derived from these sources, become operative either directly after their reception or some time later after they have been associated in their respective intracerebral centers. In the latter case, the stored impulses which serve as expressions of our psychic life or belong to the group of the emotions, need not affect solely the activity of the heart, but may also involve respiration, secretion, as well as the responsiveness of smooth and striated muscle-tissue. In general, it may be stated that pleasurable experiences decrease and annoying impressions increase the cardiac rate. It should also be noted that these afferent impulses may give rise to effects which actually endanger the life of the individual. As an example of this kind might be mentioned the so-called "reflex cardiac death" which may result whenever the inhibitor center is excessively stimulated. It should also be mentioned

¹ Hunt, *Am. Jour. of Physiol.*, ii, 1899, 395.

that while the action of the heart cannot usually be influenced by volition, certain cases are on record which clearly prove that a marked voluntary control over this organ may be acquired at times quite independently of emotional states or remote sensory impressions.¹ These volitional efforts most commonly produce an acceleration, but may also induce a slowing of the heart.

The frequency of the heart may also be lessened by exerting a slight pressure upon the vagus at any point of its course along the neck.² As this procedure is not without danger, it should only be practised with the greatest care. Augmentor or inhibitor effects frequently result from tumors or serous effusions affecting either the medulla or the cardiac nerves themselves. It should also be remembered that the activity of the cardiac center is closely related to that of the neighboring respiratory center, as is shown by the fact that the frequency of the heart increases during inspiration.³ This reaction appears in the nature of a reflex which seems to have its origin in a central stimulus rather than in one generated in the lungs themselves. Two or three reasons may be given for this view. Thus, it has been found that it persists during the spasmodic respiratory attempts following the division of the cervical portion of the spinal cord,⁴ and that it is not in evidence in certain animals. This acceleration may be made more striking by increasing the amplitude of the respiratory motions or by heightening the general irritability of the central nervous system.⁵ It has been suggested by Spalitta⁶ that the stimuli upon which this reflex depends, arise in the muscles normally employed in inspiration. Deglutition possesses a similar influence, the cardiac acceleration becoming the more marked, the greater the frequency of these movements. The opposite result may be produced by stimulating the mucous membrane of the nasal cavity with the vapors of chloroform or other irritants. This constitutes the so-called cardiac trigeminus reflex.

An intimate functional connection also exists between the heart and the systemic blood-vessels, because a higher arterial tension is generally compensated for by a lessening of the activity of this organ, while a low pressure gives rise to augmentor effects. Although the reflex character of these changes cannot be questioned, some doubt exists as to the precise locality in which these primary stimuli are produced. Thus, it may be assumed that they arise in consequence of the varying distention of the blood-vessels, but it is also possible that they are generated in the heart itself, because this organ is equipped with sensory corpuscles similar to those found in other structures.⁷ It is more than probable that the high arterial pressure tends to stimulate these

¹ Tarchanoff, *Pflüger's Archiv*, xxxv, 1885, and van de Velde, *ibid.*, lxvi, 1897.

² Thanhoffer, *Centralbl. für die med. Wissensch.*, 1875.

³ First observed by C. Ludwig (*Müller's Archiv*, 1847).

⁴ Fredericq, *Archiv de Biol.*, iii, 1882.

⁵ Henderson, *Am. Jour. of Physiol.*, xxxi, 1913, 399.

⁶ *Arch. ital. de Biol.*, xxxv, 1901.

⁷ Smirnow, *Anat. Anzeiger*, x, 1895.

end-organs by causing an overdistention of the ventricular cavities or at least of the root of the aorta. This conception finds support in the fact that even a moderate compression of the heart, as results during the act of coughing or laughing, is usually associated with an acceleration, while the irritation of the endocardium most generally gives rise to inhibitor effects.¹ Less probable is the view that these changes are occasioned by a direct action of the blood pressure upon the constituents of the cardiac center.²

One of the first proofs of the existence of these cardiovascular reflexes has been furnished by Goltz³ who found that the frequency of the heart may be reduced by simply tapping upon the surface of the abdomen of a frog with a flat instrument. As this effect is not obtained after the vagi nerves have been divided, there can be no question regarding the reflex character of these impulses. On the afferent side, their course may be either over the nerves of the cutaneous sensations or over those relegating deep sensibilities from the viscera. The latter contention seems the more probable. Very similar results are obtained in mammals in consequence of the mechanical, thermal, electrical or chemical stimulation of the abdominal viscera. Among the large number of causes for this reflex may be mentioned the accumulation of gas in the stomach or intestine,⁴ inflammatory processes or irritations of these organs by substances contained in the food, and strokes upon the region of the solar ganglia.

The cardiac acceleration commonly associated with increases in the activity of the skeletal musculature, may be explained in different ways. Thus, it may be held that the volitional impulses which are generated in the cerebral hemispheres and are then conducted to the muscles, overflow and affect the cardiac center directly. It may also be assumed that the contractions of the muscles give rise to mechanical impulses which influence the center reflexly. In the third place, it has been thought possible that the activity of the center may be varied by certain chemical substances formed in the course of muscular exercise. This view finds confirmation in the fact that the function of the center may be influenced either by varying the amounts of blood supplied to it, or by altering the oxygen content of the circulating blood. Thus, it has been found that the occlusion of the carotid and vertebral arteries, as practised by Kussmaul and Tanner, is followed invariably by a slowing of the heart. This reaction, however, does not result if the vagi nerves have been divided beforehand. Very similar effects may be obtained by lessening the oxygen content or by increasing the carbon dioxid content of the blood. Even a slight dyspneic condition suffices to augment the cardiac beats and rate, while a more intense dyspnea invariably leads to partial and complete

¹ Pagano, *Archiv ital. de Biol.*, xxxiii, 1900.

² Biedl and Reiner, *Pflüger's Archiv*, lxxiii, 1898, 385.

³ Virchow's *Archiv für path. Anat.*, xxvi, 1863.

⁴ Burton-Opitz, *Pflüger's Archiv*, cxxxv, 1908, 205.

inhibition. Very decided changes in the frequency of the heart may also be produced with the aid of the cutaneous end-organs, their activation being effected either by cold or warm water, mechanical impacts, massage, effervescent water, and other stimuli. The fact that some of these afferent impulses most easily elicit inhibitor and others accelerator phenomena, has been explained by assuming that they may be more intimately connected either with the cardio-inhibitor or with the cardio-accelerator mechanism. In the case of the carbonated water bath, however, the mechanical stimulus, consisting in the bumping of the globules of the gas against the integument, may be augmented by a direct effect of the carbon dioxid upon the cardiac center. It seems entirely probable that some of it may be absorbed and then act as a stimulant not only to the respiratory but also to the cardiovascular system.

As has been emphasized above, the cardiac center is also the recipient of sensory impulses which arise either in the membranous

FIG. 173.—RECORD OF THE CAROTID BLOOD-PRESSURE IN RABBIT DURING STIMULATION OF THE DEPRESSOR NERVE.

structures enveloping the heart, or in this organ itself. The fibers conducting the impulses from the heart are attributes of the vagus system, and have been designated by Ludwig and Cyon,¹ their discoverers, as the *depressor nerve*. These fibers become clearly recognizable upon the arch of the aorta, whence they reach the vagus center either by pursuing an independent course along the carotid artery (rabbit), or by intermingling with the vagosympathetic fibers (dog). In the rabbit, this nerve is isolated most easily in the neck, where it forms an anatomical entity next to the inner border of the cervical sympathetic and the trunk of the vagus. Centrally to this point it divides into two slender bundles, one of which enters the cervical portion of the vagus directly, and the other, the superior laryngeal branch of this nerve. The fibers of both branches then intermingle with the other vagal fibers.

¹ Berichte der sächs. Akad. der Wissensch., 1866.

The *depressor nerve* possesses a very characteristic and important function. It is sensory in its nature and conducts impulses solely from the heart to the nucleus of the vagus and the cardiac and vasomotor centers. It must be obvious, therefore, that the effects ordinarily obtained with the help of this nerve, can only be elicited by stimulating either the intact nerve or its central end. Concerning its function, it may be stated in brief that it gives rise to reflexes which are centered upon the cardiac and vasomotor mechanisms. The former produce a reduction in the frequency of the heart and the latter, a fall in arterial blood pressure. But their action upon the heart may be destroyed by dividing the vagus distally to its point of union with the depressor fibers. Naturally, the drop in pressure persists even after the division and is then frequently associated with an increase in the frequency of the heart.¹

The foregoing data show very clearly that the depressor nerve plays an important part in varying the resistance in the vascular channels against which the heart must act. To illustrate, if the arterial tension is too high, an impulse is set up in this organ which, on being relayed to the cardiac and vasomotor centers, produces a reduction in the rate of the heart and a fall in the blood pressure. Obviously, this reflex lessening of the peripheral resistance places the cardiac muscle in a much more favorable position to contract without strain.

By connecting this nerve with a string galvanometer, Einthoven² has shown that sensory impulses are generated synchronously with every contraction of the heart, but naturally, this fact does not signify that the "depressor-reflex" is elicited an equal number of times. No doubt, these impulses remain subminimal as a rule, and although transmitted to the medulla, serve here merely the purpose of maintaining the tonicity of the cardiac center. It has also been proved by Köster and Tschermak³ that electrical variations may be produced in this nerve by increasing the intra-aortic pressure artificially. Inasmuch as this nerve ramifies extensively upon the ascending portion of the aorta, it may be surmised that these sensory impulses arise chiefly in consequence of the mechanical stimulation resulting from the distention of this blood-vessel and, in a lesser degree, also from the distention of the heart itself.

¹ Bayliss, *Jour. of Physiol.*, xiv, 1893, 303.

² Pflüger's *Archiv*, cxxiv, 1908, 246.

³ *Ibid.*, xciii, 1903, 24; also see: Eyster and Hooker, *Am. Jour. of Physiol.*, xxi, 1908, 373.

SECTION IX

FUNCTIONAL PECULIARITIES OF THE CARDIAC MUSCLE TISSUE

CHAPTER XXVIII

THE ORIGIN OF THE HEART BEAT

The Excised Heart.—If the heart of a cold-blooded animal is removed from the body and is placed in a nutritive medium under proper conditions of moisture and temperature, it will continue to beat rhythmically for many hours, and even for days. Essentially the same result may be obtained with the hearts of warm-blooded animals, but inasmuch as their storative power is slight, they require a constant supply of nutritive material. Thus, it will be found that the mammalian heart ceases to beat very soon after the circulation has been interrupted, but may be made to resume its activity later on by perfusing it through its coronary blood-vessels. This procedure consists in connecting the aorta with a pressure reservoir containing an 0.8 per cent. solution of sodium chlorid, Ringer's fluid, or defibrinated blood through which bubbles of oxygen are passed at a constant rate. Under the most favorable conditions an excised heart may be kept beating rhythmically for many hours; moreover, if it is merely intended to incite the contractions without having them continue for any length of time, it is sufficient to use oil or paraffin in place of the nutritive fluids just mentioned. Evidently, the mechanical stimulus derived from the distention of the coronary vessels suffices to activate the musculature and to keep it in this condition for a moderately long time. These experiments may be repeated with smaller segments of the heart as well as with narrow strips of the ventricles. In the latter case, it is sufficient to immerse them in solutions of certain inorganic salts. Larger pieces of the ventricles may be made to beat rhythmically by perfusing them through their supply channel.

The conclusion to be drawn from experiments of this kind is that the power of rhythmic contraction is inherent in the hearts of all vertebrates.¹ Their connection with the central nervous system, therefore, is not essential to their activity and merely serves the purpose of bringing them into functional relation with the other organs and tissues.

It has previously been shown that various conditions may arise in

¹ First taught by Haller in 1757.

different parts of the body which influence the activity of the heart by way of these connecting channels. These correlating impulses, however, have nothing to do with the actual cause of the contractions. In the second place, it must be evident that even if it has been demonstrated that the beat originates in the heart, it still remains to be determined whether the impetus to contract is given by the muscle substance or by the nervous elements contained therein. The views held pertaining to this question have been embodied in the so-called neurogenic and myogenic theories of the heart beat.

Closely related to this problem is another which pertains more directly to the cause of the orderly sequence of the contractions of the different segments of the heart. Thus, it may be asserted that the rhythm of the heart is associated either with the nervous elements or with the muscle tissue. With reference to the automaticity of this organ, the question may then be raised whether its power of remaining active by a self-inducing cause is contained in the first or in the second component. At the present time it is quite impossible to give a definite answer to these questions. We are, however, in possession of certain fundamental facts relating to this topic which may best be presented separately under the headings of the theories just mentioned.

The Neurogenic Theory of the Heart Beat.—This theory which has been proposed by Volkmann, was strengthened considerably by the discovery of Remak that the heart of the frog gives lodgment to nerve fibers as well as to ganglion cells (1849). Upon entering the sinus venosus, the two vagi nerves unite to form a plexus which is situated below the pericardium and embraces numerous ganglion cells. Remak's ganglion is connected by means of two septal nerves with another network of nerve tissue which is situated in the vicinity of the auriculo-ventricular groove and is known as Bidder's ganglion. Both ganglia send non-medullated fibers to the neighboring regions of the auricles and ventricle, a few isolated nerve cells being interposed here and there. It was also noted that the apical portion of the heart, embracing the lower one-half to two-thirds of the ventricle, is free from cellular elements. Even more favorable conditions for experimentation prevail in the turtle, because the heart of these animals is larger and its nervous elements are more easily accessible.

In accordance with this theory, it is assumed that the successive cardiac contractions result in consequence of excitations which are sent out at regular intervals by the cells composing the aforesaid ganglia. Moreover, as each contraction begins near the venous entrance to the right auricle, and progresses from here toward the apex, Remak's ganglion is generally regarded as the motor center of the entire organ. It is held, therefore, that the cause of the automaticity lies within these cells, while the peripheral fibers and cellular elements serve merely as adjuncts which are made use of in the conduction of the wave of excitation to other parts of this organ. It is granted, however, that the separation of these outlying elements from the "pace-maker," enables

them to assume certain automatic properties of their own and to activate that portion of the musculature with which they are normally connected. Essentially the same explanation is given for the mode of contraction of the mammalian heart, although the location of its nervous elements has not been fully ascertained as yet.

It should be stated at this time that the neurogenic theory in its extreme form is untenable, and while a number of experiments could be cited, tending to emphasize the importance of the nervous elements as the controlling factor of the heart's action, the evidence is not sufficiently definite to prevent us from interpreting it in a way to favor the myogenic theory. The same objection, however, may be raised against several of the experiments which will be mentioned later on in support of the latter theory, because they permit of a two-fold interpretation, thus favoring one view as much as the other. The experimental evidence so far presented may be arranged as follows:

1. If the heart of a frog is removed in its entirety, it will continue to beat for a long period of time, provided, of course, that it is placed in a proper nutritive medium. If it is then cut across at the sino-auricular groove, its sinus continues to contract

FIG. 174.—HEART OF LIMULUS FROM DORSAL SURFACE. (Carlson.)

mnc, Median nerve-cord; *ln*, lateral nerve-trunks.

at regular intervals, while its auricles and ventricle cease beating at least for some time. The latter then resume their activity, the beat seemingly originating in the auricle. Their frequency of contraction, however, rarely equals the normal. If the ventricle is then separated from the auricles by a cut across the auriculoventricular groove, the latter continue to beat, while the former soon ceases its activity. A certain time having elapsed, the ventricle again contracts but now quite independently of the rhythm of the other segments of this organ.

2. Very similar results may be obtained by applying two ligatures to the heart in such a way that one comes to lie in the sino-auricular groove and the other, in the auriculoventricular groove. (Stannius experiment, 1852.) After the application of the first, the auricles and ventricle cease beating, while the sinus continues to contract. All three divisions, however, beat at regular intervals as soon as the second ligature has been properly placed and tightened. As Heidenhain has stated, the first ligature seems to exert a mechanical stimulus upon the inhibitor ganglion, while the second serves as a stimulant for the accelerator elements. It is to be noted, however, that the different segments of the heart now beat independently of one another, and that the regular progression of the wave of contraction from the sinus to the apex is no longer in evidence. These experiments tend to show that the different portions of the heart are imbued with a certain automatic power of their own which diminishes gradually in the direction from sinus to apex. This dormant power enables the more distant ganglia to originate impulses at any time after the more central elements have been destroyed or have been separated from them. Since the property of automaticity seems to be associated exclusively with nerve cells, the muscle cells find themselves in the position of mere executors of the will of a higher controlling factor.

3. By cutting and removing the nerve cord which passes along the tubular heart of the horseshoe crab, Carlson¹ has succeeded in showing that the cause of the contraction of this organ lies in the ganglion cells of the median cord, and that the conduction is effected by the nervous and not by the muscular elements. In this particular case, therefore, it would appear that the cessation of the heart beat is brought about by an interference with the automatic discharges of the ganglion cells (Weber) and not by an inhibition of the activity of the cardiac musculature (Engelmann). These results, however, do not permit of generalizations, because they cannot justly be applied to the vertebrate heart without certain modifications. The reason for this is that the heart of vertebrates may possess certain physiological properties which are very different from those displayed by the heart of the crustaceans.

4. It has been found by Kronecker and Schmey² that the regular and forceful contractions of the ventricle may be changed into mere fibrillary undulations (delirium cordis) at any time by puncturing the interventricular septum at a point near the junction of its upper and middle thirds. While this phenomenon has been interpreted as proving that the coordinated action of the ventricle is dependent upon a center situated in the aforesaid region, this hypothesis can scarcely be defended in the light of our present knowledge regarding the conduction paths of the heart. Moreover, it has been shown subsequently by McWilliams³ that the cardiac musculature may also be made to fibrillate in other ways, for example, by mechanical, thermal, and electrical stimulation of the surface of the heart in the vicinity of the apex.

5. The contractions of the mammalian heart may also be incited by perfusing the coronary circuit with non-nutritive fluids. It seems that in this particular case the distention of the coronary blood-vessels suffices to stimulate the nervous receptors in a mechanical way.

The Myogenic Theory of the Heart Beat.—This theory has been more fully developed in recent years by the work of Gaskell and Engelmann. It is held that the wave of excitation arises in the muscle tissue and that the nervous elements serve the sole purpose of correlating the action of the different parts of the heart, and secondly, of bringing the activity of this organ into functional relation with other structures. Furthermore, as the beat originates in the venous vestibule, the tissue composing this particular area, is said to possess certain functional peculiarities which render it especially suitable for the generation of those impulses which later on give rise to the contraction. The arguments favoring the myogenic theory may be cited as follows:

1. Bernstein's Experiment.—If the apical portion of the heart of a frog or turtle is separated by a ligature which is tightly drawn around the ventricle, it ceases to contract almost immediately. When isolated in this way, it may be made to beat again by applying electrical or mechanical stimuli to its surface or by raising the pressure within its cavity. The latter end may be attained at times by temporarily compressing the aortæ.

2. Strips of tissue may be cut from the apex which may be made to beat rhythmically by placing them in an isotonic solution of sodium chlorid or in Ringer's fluid. These strips frequently continue their activity for several hours. These experiments become especially significant, if it is remembered that the apex of these hearts contains no ganglion cells.

¹ Am. Jour. of Physiol., xiii, 1905, 217.

² Sitzungsber. der Akad. der Wissensch., Berlin, 1884.

³ Jour. of Physiol., viii, 1887, 296.

3. In the frog and turtle it is possible to remove practically the entire inter-auricular septum, together with its ganglia and connecting paths, without interfering with the character or rhythm of the cardiac contractions.

4. A still stronger argument is contained in the fact that the embryonic heart of the chick (2 to 5 days) or shark beat with perfect regularity at a time when as yet no ganglion cells can be made out. If segments of the embryonic heart are kept in a medium of blood plasma,¹ they will continue to beat for a long time; indeed, the muscular units usually multiply under this condition and give rise to new cells which possess rhythmic activity. While this fact clearly proves that the cardiac muscle is automatic, it may be contended that this property is primitive and of short duration, and that it is eventually superseded by the automaticity of the newly developed nervous elements.

5. The excised bulbus aortæ of the frog, and even portions thereof, usually continue to contract rhythmically. The same result may be obtained with small segments of the veins entering the sinus venosus.

6. Rhythmic contractions may be observed in the veins of the wing of the bat, as well as in certain segments of the lymphatic system. Nervous elements have not been demonstrated in these tissues.

7. In the lower forms, the wave of contraction which normally starts in the sinus portion of the heart, is propagated to the auricles and ventricles by means of clearly recognizable strands of muscle tissue. Moreover, while the conducting path in the mammalian heart, as represented by the bundle of His, is formed by a type of tissue which cannot justly be classified as muscle tissue, it does not at all possess the characteristics of nerve tissue.

8. Waves of contraction may also be incited in other parts of the heart. Thus, the stimulation of the apex most generally gives rise to a contraction in a direction opposite to normal, namely, from ventricle to sinus.

9. Engelmann has shown that the continuity of the nerve fibers of the heart may be destroyed without materially changing the sequence of its contractions. Thus, it is possible to convert the auricle of the frog's heart by several transverse cuts into a zig-zag strip without blocking the wave of contraction as it passes from the sinus to the ventricle. Very similar results may be obtained with the ventricular muscle. If changed into a zig-zag strip by transverse incisions, a contraction started in its basal portion eventually reaches the apex, while a contraction incited at the apex also progresses to the base.

The results of the experiments just enumerated indicate with certainty that the nervous elements of the heart possess the power of discharging rhythmic impulses and that cardiac muscle tissue is equipped with rhythmic properties similar to those of other tissues. Smooth muscle and, in a slight degree, also striated muscle are in possession of this power. It may be contended, however, that this primitive functional characteristic of cardiac muscle prevails only as long as no nervous tissue is present, and that it gradually loses its dominating influence in the course of the development of the latter. Thus, it may be said that the separation of the adult heart from the central nervous system or the destruction of its nervous elements again permits this primitive property of the cardiac musculature to assert itself. Arguments of this kind are difficult to meet, because, while an adequate proof of a supersedence or transfer of function of this kind is not at hand, no perfectly definite reasons can be given against this occurrence. It seems best, therefore, to leave this matter

¹ Burrows, *Science*, xxxvi, 1912.

in abeyance, with the understanding, however, that the evidence so far submitted favors the myogenic theory.

The Nature of the "Internal" Stimulus.—Even if the cause of the heart beat should finally be localized either in the nervous tissue or in the muscle tissue, the nature of the exciting agent must still remain doubtful. It is customary to evade this question by saying that the cardiac muscle possesses the power of automaticity, the implication contained in this statement being that this tissue embraces certain excitatory agents which are capable of acting independently of outside influences. Strictly speaking, however, this cannot be true, because all reactions of living substance are dependent upon material brought to it from the outside. Without stimuli of this kind life is impossible.

In seeking to discover the nature of the "inner" stimulus, it is fair to assume that the cardiac contractions result in consequence of an interaction between the chemical constituents of the blood and those of the substance of the heart. If this problem is restricted in this way, further advance in this direction necessitates the determination of those substances which act as exciting agents either individually or when combined with others. In what measure we have succeeded in isolating these agents will be brought out in the succeeding paragraphs.

It is a well-known fact that the hearts of the cold-blooded animals continue to beat for some time after their excision, while the hearts of the warm-blooded animals cease their activity very soon after the interruption of the circulation. Both types of organs, however, may be kept in an active condition outside the body by supplying them with defibrinated blood or some other nutritive fluid. This difference in their behavior may best be explained upon the basis of metabolism. As the mammalian heart possesses a more vivid metabolism, it requires a more constant supply of nutritive material, and especially, because its storative power is altogether too slight in comparison with the work demanded of it. It is essential, therefore, that it be in possession of an extensive coronary system which enables even its most remote cellular constituents to obtain fresh substances in a very brief time. The heart of the lower animals, on the other hand, does not require a system of local blood-vessels, because its metabolic processes are less intense and are amply safeguarded by direct interchanges with the blood as it traverses its cavities. The cells of the lower hearts also seem to be able to store a considerable portion of their nutritive material, so that it may be made use of whenever the blood supply is cut off.

It has been found by Merunowicz that an aqueous extract of the ash of the blood exerts a stimulating action upon cardiac muscle. In continuation of these experiments Ringer¹ has proven in 1882 that certain inorganic salts, namely the chlorids of sodium, calcium and potassium, affect this tissue in a very specific manner, because they are especially adapted for maintaining the beat. In the case of the heart of the frog, these salts act most efficiently in the following concentration:

¹ Jour. of Physiol., iv, 1883, 222.

NaCl.....	0.65 per cent.
KCl.....	0.03 per cent.
CaCl ₂	0.25 per cent.

Even the mammalian heart may be kept beating for many hours by perfusing it with this solution. The best results, however, are obtained if the solution is first charged with oxygen before it is allowed to enter the coronary vessels. Locke¹ recommends a perfusion fluid containing 0.9 per cent. of NaCl, 0.024 per cent. of CaCl₂, 0.042 per cent. of KCl, 0.01–0.03 per cent. of NaHCO₃, and 0.1 per cent. of dextrose. This fluid should be warmed to 35° C. and charged with oxygen. The dextrose is said to prolong the period of contraction and to renew the vigor of those hearts which have ceased to beat while still being perfused with the pure solutions of the aforesaid salts. With the aid of this solution, Locke and Rosenheim² have succeeded in reviving the isolated heart of a rabbit on four consecutive days, keeping it in activity each time for several hours. In a similar way, Kuliabko³ has been able to incite contractions in a rabbit's heart three and four days after its removal from the body. Hering⁴ revived the heart of a monkey 28 and 54 hours after the death of the animal. Very similar results have been obtained with human hearts.

FIG. 175.—TRACING OF CONTRACTIONS OF A FROG'S HEART, SHOWING EFFECT OF ADDING A TRACE OF CaCl₂ TO THE NaCl SOLUTION USED PREVIOUSLY FOR PERFUSION. (Ringer.)

It is evident, therefore, that these salts give rise to an osmotic environment which is well adapted for cardiac muscle. The action possessed by each salt individually, has been brought out by the work of Kronecker,⁵ Howell,⁶ Loeb⁷ and others. By making use of strips of the ventricle of the frog or turtle, it has been shown that the preceding solution is capable of inciting a rhythmic activity which may last for many hours. The same end may be attained by immersing these preparations in a 0.7 per cent. solution of sodium chlorid. The contractions appear as a rule after a latent period lasting from 5–20 minutes, and attain a maximal height and length in the course of a few minutes. It is to be noted, however, that while this salt excites the contractions, it does not maintain the beats for any considerable length of time. The muscle presently ceases its activity in the state of relaxation. The sodium salt, therefore, favors contractility and irritability. If a small quantity of a solution of calcium chlorid is now added to the former in slight excess of the sodium, the strip of muscle again begins to contract. Later on, however, its contractions become more and more forced until it remains in a condition of tonic shortening, known as calcium rigor. By the addition of a small amount of potassium chlorid, this strip may then be activated again. An excess of potassium, however, leads to a slowing and a possible cessation of the contractions. The muscle is then retained in a state of extreme relaxation.

¹ Jour. of Physiol., xviii, 1895, 332; also see: Mines, *Ibid.*, xxxvii, 1908, 408, and xlii, 1911, 251.

² *Ibid.*, xxxvi, 1907, 205.

³ Pflüger's Archiv, xevii, 1903, 539.

⁴ *Ibid.*, cxvi, 1907, 143.

⁵ Festschr. für C. Ludwig, 1874.

⁶ Am. Jour. of Physiol., ii, 1898, 47.

⁷ Festschr. für Fick, 1899.

While the sodium, calcium, and potassium may not be the only agents concerned in this excitation, it must be evident that they play a most important part in the formation of a molecular concentration of the blood which favors the activity of cardiac tissue. It must also be apparent that these salts are specific in their action. The sodium, for example, stimulates contraction, while the calcium maintains the tonus and the potassium favors relaxation. Obviously, therefore, a proper activity of the heart can only be secured by means of a solution which contains these salts in perfectly definite proportions. Howell, in fact, believes that the states of contraction and relaxation of cardiac muscle are dependent upon an alternate and opposing interaction of these substances with the contractile elements of this tissue. In this connection, it is of interest to note

FIG. 176.—A FROG'S HEART POISONED BY EXCESS OF CALCIUM SALTS, RECOVERS ITS SPONTANEOUS RHYTHM ON ADDING A TRACE OF KCL TO THE PERFUSION FLUID. (*Ringer.*)

that Biedermann¹ and Loeb have succeeded in eliciting rhythmic contractions in striated muscle by subjecting it to the influence of isotonic solutions of sodium and lithium. Solutions of calcium, on the other hand, have been proved to possess an inhibitor action.

As far as the nature of the "inner stimulus" of the heart is concerned, it may be held that the substances just enumerated, actually constitute the exciting agent (Howell), or that they merely furnish a medium in which the true stimulus is then capable of unfolding its action (Engelmann). If the latter view is adhered to, the stimulating agent, whether it be chemical, electrical, or enzymotic in its nature, has not been discovered as yet.

CHAPTER XXIX

THE PHYSIOLOGICAL PROPERTIES OF CARDIAC MUSCLE

Refractory Period. Extrasystole.—The heart of the lower animals may be made to register its contractions upon the paper of a kymograph by connecting its apex with the free end of a writing lever. A thread and small hook are used to make this connection. Another procedure is to place a delicate rod upon the ventricle and to permit it to act against the long arm of a writing lever. The lower end of this rod should be equipped with a cup-shaped platelet serving to retain the former more firmly upon the surface of the heart. A third method

¹ Wiener Sitzungsber., lxxxii, 1880.

consists in fastening the apex of the ventricle to the long arm of a writing lever, which is pulled upward beyond its horizontal position by a counter spring (Fig. 177). In the latter case, the contracting ventricle pulls the lever downward, while in the first two instances the lever moves upward during systole and downward during diastole.

Under normal conditions, the successive up and down strokes are of equal size, but assume a smaller amplitude as soon as the prepara-

FIG. 177.—SCHEMA TO ILLUSTRATE THE METHODS OF RECORDING THE CONTRACTIONS OF THE FROG'S HEART.

The writing lever (*W*) is pulled upward by a spring (*S*) against the action of the heart.

tion becomes fatigued or when it is made to act under less favorable circumstances (Fig. 178). Very similar records may be obtained with apex-preparations subjected to electrical stimuli or with strips of ventricular muscle immersed in a solution of the inorganic salts. It is to be noted, however, that the amplitude of the contractions cannot be changed by varying the strength of the stimuli. This fact

FIG. 178.—RECORD OF THE CONTRACTIONS OF THE FROG'S HEART.

The time is registered in seconds.

implies that a heart always contracts with full vigor irrespective of the character of the stimulation. This result is somewhat different from that ordinarily obtained with striated and non-striated muscle, because the reactions of these tissues are directly proportional to the strength of the stimuli. Cardiac muscle, therefore, is said to behave in accordance with the "*all or none*" law, *i.e.*, it always reacts maximally, whether the stimulus be slight or strong.

In explanation of this phenomenon, it should be mentioned that Gotch and K. Lucas¹ have shown that the amplitude of the contractions of striated muscle is determined by the number of fibers actually involved in this process. In other words, while a slight stimulus activates only a relatively small portion of the total mass of the muscle, a strong stimulus causes a much more general reaction. The cellular components of heart muscle, however, are not functionally independent of one another, and hence, are not adapted to give graded reactions. Thus, even the slightest stimulus must produce a wave of excitation which spreads far and wide through its different rows of cells and involves even its most distant constituents. This explanation of the "all or none" law permits of the conclusion that the mode of contraction of cardiac muscle is not at variance with that of other contractile tissues. It must be evident, therefore, that the functional difference to which attention has just been called, is dependent upon the number of the cellular units involved and not upon any chemicophysical differences in the muscle substance. Consequently, the all or none law merely serves to show that the different components of cardiac muscle are more closely allied with one another than those of skeletal muscle. It is easily noted, however, that this continuity is not the same in all hearts, as is shown by the fact that the effects in those of the frog, turtle and different mammals always possess a disseminating character, while those obtained in the crustacean heart do not. Regarded from the standpoint of hemodynamics,² a maximally contracting heart is of course to be preferred, because it gives rise to more uniform discharges and more constant pressures.

The assumption that cardiac muscle is a functional curiosity, is disproved further by the fact that it gives rise to the phenomena of *summation of stimuli* and *summation of contractions*, both of which are conspicuous characteristics of skeletal muscle. Thus, it has been found that if several subminimal shocks are sent into a quiescent strip of frog's ventricle in rapid succession, these individual stimuli are added to one another until they finally give rise to a contraction. Furthermore, if the ventricle of a Stannius-heart is stimulated with single shocks at the rate of one in every ten seconds, the first reactions frequently tend to be somewhat smaller than those obtained later on, so that an ascending series is produced, resembling the "staircase contractions" of striated muscle. This result is obtained only under experimental conditions and, hence, does not run counter to the "all or none" law.

In accordance with the well-established fact, that a mass of living substance cannot continue to react unless a sufficient time be allowed it during which to replenish the material destroyed during its preceding period of activity, it may justly be assumed that the successive systolic and diastolic phases of the heart represent period-

¹ Jour. of Physiol., xxxviii, 1909, 113.

² Woodworth, Am. Jour. of Physiol., viii, 1902, 213.

ically recurring catabolic and anabolic phenomena. No doubt, the systolic movements necessitate the utilization of the largest store of its energy-yielding material which must first be replaced before the next contraction can take place. The systole, therefore, must be considered as the period of decomposition of the contractile substance and the diastole as the period of assimilation. Moreover, as the irritability of all tissues depends upon a proper store of energy-yielding substances, the power of cardiac muscle to respond to stimuli must be at a minimum when catabolic processes are going on. This is the case during systole. The stimulus to contract is given immediately preceding this period. This implies that certain chemicophysical changes result at this moment which eventually give rise to the visible contraction. During systole, however, while the heart is thus engaged in converting practically all its potential energy into kinetic energy, no other excitation can be brought to bear upon it effectively. This means that it is then in a non-responsive state and is, so to speak, impermeable or refractory to outside influences. Immediately upon the completion of its *refractory period*, it again becomes receptive and more so later on in the course of diastole. Its greatest irritability it attains just before the next contraction.

These changes in irritability may be detected very easily if single induction shocks are passed through the heart of a frog or turtle at any time while it registers its contractions upon the paper of a kymograph.¹ It will be noticed that a stimulus which reaches it during its systolic state, does not alter the sequence nor the general character of its contractions, whereas a stimulus which enters at the very beginning or at any time during the diastolic period is followed by an *extrasystole*. This extra contraction, however, does not appear until the succeeding normal one has been completed. In accordance with what has just been said, it must be clear that a greater strength of stimulus is required to produce this second reaction when applied at the beginning of the period of relaxation than when applied near its end. This difference, as we have just seen, is accounted for by the fact that the restoration of the contractile substances has been practically completed at the end of diastole. The height of these extrasystoles corresponds very closely to that of the normal contractions.

After the completion of an extrasystole, the heart most generally remains in a condition of relaxation during the interim of one beat. It then exhibits a so-called *compensatory pause*. This designation, however, is not especially pertinent, because this temporary inhibition does not serve the purpose of compensating for the preceding hyper-effort, but only to correct the disturbance in the rhythm. The correctness of this statement may be proved without much trouble by studying these extra contractions when generated in an isolated ventricle. If this portion of the heart, or a strip thereof, is activated by subjecting it to the stimulating influence of a solution of the inorganic salts, these

¹ Marey, Trav. du laboratoire, 1876.

extra contractions may then be incited without giving rise to compensatory pauses, nor do we then obtain a significant disturbance of the rhythm. It seems, therefore, that this phenomenon can only develop in the spontaneously beating heart, the activity of which, as we have seen above, is dependent upon rhythmic discharges from the "pace-maker" situated at the venous vestibule. Under normal conditions, these stimuli are generated at regular intervals and activate the auricles and ventricles in quick succession. The latter in particular are well

FIG. 179.—TRACINGS OF SPONTANEOUS CONTRACTIONS OF FROG'S VENTRICLE, TO SHOW REFRACTORY PERIOD.

In each series the surface of the ventricle was stimulated by an induction shock at E, as indicated by the tracing of the signal. In 1, 2 and 3 this stimulus had absolutely no effect, since it fell during the refractory period. In 4, 5, 6, 7 the effect of the shock was to interpolate an extra contraction in the series, the latent period (shaded part) gradually diminishing from 4 to 7 (diastolic rise of irritability). In 8 the irritability of the preparation was already considerable, and the latent period inappreciable. The "compensatory pause" after the extra beat is also well shown in 4, 5, 6, 7, 8. (*Marey.*)

supplied with contractile substances, and are therefore very irritable and responsive. If they are now made to give an extrasystole, the subsequent normal wave of excitation must arrive in them at a time when they are just engaged in producing this contraction. Consequently, they are impermeable to this stimulus and refractory. Inasmuch as this excitation remains without results, the ventricles continue inactive during the period ordinarily occupied by the next normal contraction. The succeeding normal wave of irritability, however,

finds the ventricle again in a receptive state and is therefore able to incite a contraction. No further disturbance takes place until another extrasystole is interposed.

The refractory period and compensatory pause serve as a protective mechanism which prevents any interference with the cardiac rhythm. But if such a condition has actually arisen (arrhythmia), their tendency will be to reestablish normal relationships as quickly as possible. In addition, the refractory period serves to check off the individual discharges of the "pace-maker" and to regulate the length of the successive systoles. Under ordinary conditions, therefore, the latter must retain a twitch-like character and cannot become tetanic. It is possible, however, to prolong them unduly either by stimulating the heart with a series of strong induction shocks, or by exposing it to heat.

FIG. 180.—ELECTROCARDIOGRAM SHOWING AN EXTRASYSTOLE AT E, AND COMPENSATORY PAUSE AT C. (Cunningham.)

Extrasystoles are frequently encountered in the human heart without being able to recognize a distinct lesion of the myocardium or of the conducting paths. No special importance need be attached to them as long as they remain infrequent. Most commonly they find their origin in a hyperirritability of the local or general nervous elements. Two types of extrasystoles are recognized clinically, namely, those which are followed by a distinct compensatory pause and those which are not. The former are more common and are often designated as *premature beats*. They result in consequence of impulses which start either in the pace-maker itself or high up in the conducting paths and adjoining auricular tissue. The latter are generally called *interpolated systoles*, and seem to be due to stimuli which originate either in the substance of the ventricles or in the more distal segment of the conducting bundle. For this reason, they cannot seriously interfere with the regular waves of excitation conveyed downward from the auricle and, hence, cannot give rise to a distinct compensatory pause or

a disturbance of the rhythm. It might also be mentioned that a large number of the so-called "premature" beats are caused by impulses which arise in a hypersensitive auricular tissue. Whether these stimuli originate in this particular area or nearer the pace-maker, can readily be determined by noting the length of time intervening between them and the next systole, because a compensatory pause must arise as soon as the distance between their place of origin and the ventricle becomes sufficiently great to allow them to reach the latter while in systole. The method of auscultation is not well adapted for the detection of these irregularities in rhythm, and especially not if they are of the interpolated type, but it is possible to recognize them without difficulty with the aid of the electrocardiograph.¹

The Tonus of Cardiac Muscle.—The functional capacity of the heart depends upon the tonus of its muscular elements. This fact implies that the latter are normally held under a certain physiological tension, *i.e.*, they are retained in a state intermediate between complete relaxation and contraction. The tonus, however, does not remain the same for a long period of time, but varies with the character of the internal stimuli. This fact may readily be deduced from any continuous record of the beating heart of a frog, because the curve as a whole does not follow along a straight horizontal line, but shows long wave-like oscillations. In this respect, cardiac muscle does not differ from striated or non-striated muscle tissue, because both of these are continuously exposed to tonic impulses and are able to relax fully only if separated from the central nervous system. It need scarcely be emphasized that a muscle when held in a position of partial contraction, can reach the condition of maximal shortening with much greater rapidity. This statement also applies to the arteries and other tubular organs, because their walls are ordinarily kept in a position intermediate between constriction and dilatation.

The property of tonicity of a tissue is dependent upon the activity of the nervous elements with which it is connected. It is believed that the nervous centers give origin to a series of subminimal impulses which tend to keep the tissue continually in a condition of functional alertness. Concurrently, it may be reasoned that if these impulses are prevented from reaching their destination for any length of time, the tissue loses its tonicity and eventually becomes functionally useless. In the case of the isolated heart, however, the tonus is retained in a measure, because its intrinsic nervous elements are capable of generating those impulses which under normal conditions are derived from its extrinsic centers.

The nature of the stimuli upon which the tonus depends is still unknown. It is commonly held that the tonicity is due to the same stimuli which produce the contractions. In the former case, however, they remain subminimal, while in the latter case they become supra-

¹ Lewis, *Clinical Disorders of the Heart Beat*, London, 1913.

minimal. Fano,¹ on the other hand, believes that there are two different kinds of excitatory agents at work. In support of this contention, Gaskell and Mines² have found that weak acids and carbon dioxid diminish the power of contraction as well as the tonus, whereas an increased alkalinity gives rise to just the opposite effect. It seems certain, however, that an optimum degree of tonus can only be obtained if the body fluid possesses a perfectly definite reaction. As the reaction of the blood depends chiefly upon the tension of carbon dioxid, it may be inferred that this gas plays a most important part in the production of tonicity.³

It must be clear that the tonicity of cardiac muscle furnishes a means of determining its functional capacity. Under ordinary conditions it is sufficient to note the amplitude and force of the contractions of the exposed or isolated heart, or to measure the pressure which the normally beating organ is capable of developing in the blood-vessels. To begin with, the individual cells must of course be capable of entering the state of complete relaxation, as well as that of maximal contraction. Hence, they must possess a wide range of movability. The former quality is as important as the latter, because it determines the capaciousness or power of filling of the entire organ. It must be evident that a loss of the relaxing power of the muscular units must place the heart under a certain disadvantage, because it lessens the capacity of its chambers. Quite similarly, it may be said that an unusual degree of relaxation must act unfavorably, because it tends to invite an undue distention and imperfect emptying of the cardiac chambers. The latter condition indicates a loss of tonus approaching fatigue, and may lead to a general dilatation of the organ when called upon to perform an extra amount of work. It stands to reason that a muscular unit which is not tonically set is not in a favorable position to resist those strains which frequently arise in the vascular system in consequence of physical exertions and emotions. A loss of tonus, therefore, exposes the heart to the danger of becoming hyperdistended and dilated.

Opposed to the condition of dilatation is the condition of hypertrophy, which presents itself in the form of either a deposition of perfectly new cells or an increase in the volume of those already present. In either case, an organ larger and heavier than normal is the result. Hypertrophy finds its origin in the fact that the cardiac cells are in a tonic condition and react to excessive stimulation by increasing their power of contraction. This change eventually produces a compensatory increase in the size and massiveness of the heart, while the condition of dilatation is a simple distention without a deposition of new material. But it is not always true that these changes affect the organ as a whole, in fact, in many instances only single compartments are involved. Thus, mitral stenosis is usually associated with a hypertrophy of the left auricle and aortic stenosis with a hypertrophy of the left ventricle.

¹ Festschr. für C. Ludwig, Leipzig, 1887.

² Jour. of Physiol., xlv, 1913, 23.

³ Patterson, Piper and Starling, Jour. of Physiol., xlviii, 1914, 465.

The ability of cardiac muscle to increase its substance is of great dynamical importance, because in the absence of this compensation grave circulatory disorders would result. In illustration of this statement, attention might briefly be called to the different lesions of the cardiac valves, which may persist for many years without serious impairment of the circulation. A stenotic condition of one or the other of the cardiac orifices commonly produces a hypertrophic condition of that part of the heart which forces the blood through this opening. In this way, the supply of blood to the compartment situated distally to the obstruction may be kept practically the same for many years. This is also true in a way of regurgitation, because the continuous stretching of the cardiac chamber by the regurgitating blood serves as a stimulus for its elements to contract more forcibly. In both cases the arterial pressure and flow remain practically normal until the primary lesion has developed sufficiently to exceed the limit of this physiological compensation.

SECTION X

THE MECHANICS OF THE CIRCULATION.

HEMODYNAMICS

CHAPTER XXX

PHYSICAL CONSIDERATION

The Sources of Pressure.—If considered from the kinetic or dynamic standpoint, the movements of fluids may be said to be dependent upon the force of pressure, which in turn is derived from three sources, namely from:

1. An outside factor (hydraulic pressure).
2. Imparted motion (hydrodynamic pressure).
3. The weight of the fluid (hydrostatic pressure).

In a similar manner it may be stated that the flow of the blood finds its cause in the pressure to which it is subjected while traversing the vascular channels. This force, as has just been emphasized, must be regarded as the product of three factors, although it cannot be doubted that in this case the dynamical action of the heart is the most important of the three.

Hydraulic influences are brought to bear upon a fluid from without. A condition of this kind may be produced either by permitting oil or mercury to press upon water or by subjecting the fluid contents of a syringe or of a hydraulic pump to pressure by means of a piston. In all these cases, the fluid must be confined in a closed receptacle, or must be kept under such conditions that its chances of escaping to the outside are so slight that a general displacement of it cannot result. The vascular system fulfills these mechanical requirements very efficiently, because its channels are closed and are sufficiently elastic to yield to pressure. The degree of their distention, however, is not sufficiently great to neutralize the pressure. In this case, the heart takes the place of the piston and the capillary bloodbed, that of the narrow outlet. **Hydrodynamic influences** are brought into play in so far as every moving fluid is in possession of a certain kinetic energy which tends to drive it onward, even at a time when the external force has ceased to act upon it. At this moment, one component of the fluid presses upon the one ahead of it, and so on, until the end of the column has been reached. **Hydrostatic influences** are also present, because every fluid possesses weight, and hence, its lower layers are always subjected to the pressure of its overlying strata.

In determining the degree of pressure exerted by these forces, the following facts should be kept in mind. The pressure of the air resting upon the surface of the earth, amounts to about 1 kg. per square cm. of area. This volume of air weighs 1033 gm. This pressure which is designated as one atmosphere, may be

counterbalanced by any factor capable of exerting precisely the same degree of pressure. If water is used for this purpose, it would have to be 1033 cm. in height, provided its specific gravity is unity. If mercury is employed instead, a column only 76 cm. in height would be required, because the specific gravity of this element is 13.55 times greater than that of water. When a pressure exceeds that of the atmosphere, it is rated as positive, and when it is less than the atmospheric, as negative. Thus, the values of the pressures prevailing in the different channels and cavities of our body, are always rated in accordance with the line of the atmospheric pressure (760 mm.). This constitutes the zero line or abscissa.

Dynamically considered, blood behaves in much the same way as water. It flows through the vascular channels in agreement with certain laws which are derived from those regulating the flow of other practically incompressible liquids. One difficulty, however, is met with and that is the distensible and elastic character of the blood-vessels and spaces. For this reason, it must be admitted that

the general physical data given above, may not be applicable to the conditions encountered in a circulatory system built up of living matter. In spite of this probability, however, it seems advisable to give a brief discussion of the factors controlling the flow of a fluid through rigid tubes, because many of the problems connected with the circulation of the blood are founded upon them. But as our knowledge regarding the dynamics of the movement of liquids, or hydrodynamics, is still very incomplete, the present discussion must be restricted to the simplest of the facts known.

FIG. 181.—DIAGRAM ILLUSTRATING TORICELLI'S THEOREM.

h , height of pressure; R , resistance at orifice..

Toricelli's Theorem (1643).—If a fluid is placed in a receptacle possessing vertical and parallel walls, it exerts a pressure upon the lower surface of this vessel equal to the weight of any other mass of fluid of the same cross-section and height. If a round opening is now made in the bottom of this reservoir, while the quantity of

fluid within it is replenished sufficiently to remain at the level (h), the fluid escapes with a velocity (v) which may be expressed by the formula: $v = \sqrt{2gh}$, g being the acceleration produced by the gravity. It is a well-known fact that the speed attained by a falling body equals $2gh$, and hence, the velocity of a fluid flowing through a hole in the bottom or side of a receptacle, is the same as that attained by the fluid when falling *in vacuo* through the distance (h). Thus, it should be possible to determine with accuracy the volume of the fluid escaping in a unit of time, by contrasting the velocity with the cross-section of the outlet. It has been shown, however, that the quantity of fluid which may be expected to escape upon theoretical grounds, does not quite equal the quantity obtained. This discrepancy is caused by the resistance encountered by the fluid at the brim of the orifice (r). As only a limited number of columns of fluid lie in straight lines vertically above the opening, the others must occupy positions lateral to these. But as the latter tend to escape together with the former, they must converge toward the center of the orifice, so that a conical and not a cylindrical outline is imparted to the entire mass of outflowing liquid. Consequently, the total energy (h) cannot be spent to produce velocity, because some of

it is required to overcome the resistance at the outlet. Obviously, therefore, the formula deduced by Toricelli, holds true only if the resistance to the outflow is so slight that it can justly be neglected.

Flow of a Liquid Through Rigid Tubes.—Further modifications of the previous contention are made necessary if the orifice of the receptacle is equipped with a round tube of uniform diameter, adjusted in a horizontal direction. It must be evident that this addition places an even greater resistance in the path of the escaping fluid, thereby insuring a still greater reduction in the outflow. It is essential, however, that the size of the tube do not exceed a certain limit, because, if it possesses a very large diameter, the conditions of flow become so complicated that they cannot be brought in accord with our present knowledge pertaining to this matter. Moreover, theoretical speculations of this kind seem uncalled for at this time, because channels of exceptional diameter are not encountered in the vascular system.

A liquid flowing through a tube, always meets with a certain resistance which is dependent, on the one hand, upon the cohesion of its molecules, and, on the other, upon the adhesion of its outer layer to the walls of the vessel. The former constitutes the internal friction or viscosity, and the latter, the external friction. Provided, therefore, that a liquid moistens the vessel wall, an adhesion results, in consequence of which its outermost layers become stationary. The molecules of the layers of fluid situated next to the outermost, are also retarded by cohesion, but they are not stopped altogether. The more centrally situated layers are slowed in quite the same manner until the axial column is reached which, however, is retarded least of all and possesses therefore the greatest speed of flow. When speaking of velocity, we generally refer to the average speed attained by a liquid irrespective of the differences shown by its various layers. Furthermore when dealing with straight tubes which impart a parallel motion to the different particles of the liquid, the general velocity of the flow is only one-half as great as that of the axial stream. Obviously, therefore, the pressure of the liquid in the reservoir is constantly made use of in overcoming the peripheral resistance composed of the forces of adhesion and cohesion. Thus, while a part of the static energy produced by the mere position of the liquid, is consumed in antagonizing this hindrance to the flow, the remainder is converted into kinetic energy, as evinced by the escape of the liquid from the tube.

The resistance to the flow is betrayed by the *lateral or side pressure* prevailing at the different points of a system of tubes. Thus, if a number of vertical tubes, or piezometers, are connected in series with the main horizontal channel, some of the liquid escapes from here and enters these branches to a height corresponding to the pressure prevailing at these points. In other words, the level of the liquid in these laterals is accurately adjusted to the peripheral resistance encountered by the liquid as it passes these points. It must be clear that the liquid exerts a certain pressure upon the internal wall of the main tube which is evenly distributed in all directions. Besides, if the main channel is equipped with a branch, the pressure prevailing in the former, is propagated outward through the orifice in its wall in strict agreement with the cross-section of the collateral. Under this condition, the internal pressure is capable of supporting in the side-tube a column of liquid of a certain height or weight. By determining the latter (h), an accurate measure is obtained of the pressure prevailing at the point where the branch joins the main tube. Furthermore, since the resistance in a tube of uniform diameter is proportional to its length, and since the resistance still to be overcome diminishes with the proximity of the outlet, the pressure must decrease gradually in a direction from the reservoir to the outlet. For this reason, the occlusion of the latter

is immediately followed by a rise of the liquid all the way to the reservoir, because under this condition the collaterals are converted into mere recesses of the main vessel.

It must be clear, therefore, that the power furnished by the liquid in the reservoir (H) is the downward pressure of its constituents. A large portion of it (h) is utilized in overcoming the resistance and is therefore known as the *resistance-pressure*. The remainder (h') constitutes the actual driving force and is commonly spoken of as *velocity-pressure*. The amount of each may be determined very readily by joining the levels of the liquid in the piezometers by a straight line and by extending this line until it meets the reservoir ($y-n$). It should be noted, however, that their sum total is not absolutely equal to the *head-pressure* (H). This discrepancy indicates that a fraction of the latter (x) is used up in overcoming the friction encountered by the liquid in its passage through the orifice of the reservoir. The initial energy (H) may also be produced in other ways than by means of the position or "head" of the liquid in a reservoir, for example, by the movement of a piston within a cylinder. But the results remain the same irrespective of the source of the pressure.

FIG. 182.—A PRESSURE VESSEL, P , WITH A HORIZONTAL OUTFLOW TUBE, $O-n$, INTO WHICH VERTICAL TUBES OR MANOMETERS ARE INSERTED (a, b, c, d, e , and f).

If the tube attached to the reservoir, does not retain the same diameter throughout, but changes from large to small, or from small to large, the dynamical conditions resulting therefrom may readily be deduced from the foregoing data. Thus, if the median portion is the larger, the speed of flow is diminished in this particular segment, because the velocity is inversely proportional to the cross-section. Moreover, in as much as the resistance is less here, the initial energy or head-pressure is used up more slowly in this section. Consequently, the lateral pressure declines less rapidly here than nearer the reservoir. On entering the third segment which possesses the same diameter as the first, the original velocity is again established, while the increased resistance in turn insures a more rapid fall in pressure.

If a tube is now used, the second segment of which is narrower than the first and third, the speed of flow is increased in the central one. This implies that the resistance is also increased, while the head pressure is considerably diminished. This change is clearly indicated by the fall in the lateral pressure. On reaching the third section of the tube, the velocity and resistance are decreased as is betrayed by a less rapid fall in the pressure. In the preceding experiments the head-pressure has always been kept constant by making provision for a steady influx of water into the reservoir to compensate for its outflow. But if the initial energy

is not exerted continuously, the fluid will escape from the distant orifice of the tube only when a definite quantity has been forced into its central end. Under this condition, the outflow becomes intermittent, although it does not cease as yet at the very moment when the pressure is discontinued. It lags behind, because its inherent sluggishness causes it to escape with a rapidity which is less than that of the influx.

Flow of a Liquid Through Elastic Tubes.—If the rigid tube is displaced by one possessing elastic walls, a condition of flow will be established in time which is practically the same as that described previously. To begin with the walls of the tube move outward in the direction of the lateral pressure exerted by the liquid, and this distention continues until the elastic power of the walls exactly counterbalances the internal pressure. At this time, the elastic tube really displays the same phenomena as those previously observed in the rigid system, but naturally, only as long as the head-pressure remains constant. If the latter is diminished, the vessel wall must first recoil to adapt itself to the new conditions.

If the head-pressure is now permitted to act intermittently, the conditions of pressure and flow must be the result of the force and frequency with which the primary power is applied and secondly, of the resistance which this primary power encounters in the system of tubes. To begin with, let us suppose that the pressure acts at long intervals and that the resistance is slight. The latter condition may be produced without difficulty by using a short tube of relatively large diameter. In this case, the entrance of the fluid is associated with a distention of the walls of this tube and a discharge from its outlet which is greatest during the period of highest pressure, and becomes less and less as the driving force is diminished. A flow of this kind is characterized as intermittent. If the pressure is now allowed to act more frequently, or if the resistance is heightened, or both, the outflow becomes smaller during the interims, but does not cease altogether. The flow is then said to be remittent. By continuing to increase the force and frequency of the pressure, as well as the resistance, a point will finally be reached when the outflow ceases to fluctuate. It is then constant in its character.

If a certain quantity of liquid is permitted to escape from the reservoir into the elastic tube, the walls of the latter are forced apart. The influx having ceased, the walls tend to come together again. This recoil is a property of all elastic bodies. If the pressure is now applied more frequently, while the resistance is permitted to remain the same or is increased, the mass of the liquid in the tube increases steadily. This is made possible by the steady yielding of the walls of the tube in an outward direction. The tube is distended. Eventually, however, its elastic recoil effectively counteracts all further distention and storage of liquid. It must be evident, therefore, that the quantity of fluid which is present in the tube in excess of that constantly escaping through the outlet, is sufficient to maintain a certain pressure even during the intervals of time when the head pressure is not being exerted. In this way, the fluid is held under a continuous pressure with the result that the outflow remains practically constant. Thus, it will be seen that the property of elasticity by means of which the walls of the tube endeavor to regain their original position, is of greatest importance to the agent producing the pressure, because it helps to preserve normal conditions of flow even during the periods when the latter is at rest. Obviously, therefore, the energy developed by the generator is stored each time in the walls of the tube in the form of elastic tension. It is then spent during the periods when the primary force is not acting. In this way, the flow is kept constant in spite of the fact that a new supply of fluid is had only every now and then.

Analogous Features of the Circulation of the Blood.—Essentially the same conditions prevail in the vascular system. The heart which here assumes the function of the rhythmically discharging reservoir or piston pump, contracts and forces a certain quantity of blood into the vascular channels. The frequency of this organ, as well as the peripheral resistance, is adjusted in such a way that the blood-vessels are constantly retained in a condition of hyperfilling, made possible by the elastic tonicity of their walls. In this way, the intermittent ventricular discharge is converted into a continuous flow. The power of the heart is transferred each time into elastic tension. The latter acts while the heart is at rest.

FIG. 183.—PRESSURE VESSEL WITH PROGRESSIVELY BRANCHING TUBES WHICH ARE AGAIN UNITED INTO ONE COLLECTING CHANNEL.

This arrangement illustrates the conditions prevailing in the vascular system. (*Brubaker.*)

If it were not for the fact that the diameters of the different blood-vessels vary considerably, the pressure prevailing in the vascular system would be practically identical with that existing in a system of tubes such as has been represented in the preceding schema. In reality, however, the central arterial trunk or aorta, divides again and again into much smaller branches which eventually give rise to the capillaries. Beyond this point, these fine tubules constantly unite into larger ones until the venæ cavæ and right side of the heart have been reached. This multiple division brings it about that the total cross-area of the vascular system is steadily increased from the arteries to the capillaries, while beyond these tubules, it is again gradually diminished. For this reason, these conditions of pressure and flow must closely resemble those described in one of the earlier paragraphs dealing with the dynamics in tubes of varying diameter. To

illustrate, as the cross-section of all the capillaries put together is larger than that of either the arteries or veins when combined into single tubes, the lateral pressure as well as the velocity of flow must be much less in these tubules than in the latter channels. Besides, as the friction in these exceedingly fine tubules is considerable, they really serve the purpose of a resistance which is interposed at this point of the vascular system to retard the flow of the blood. On account of this hindrance, the arterial blood is held back, thereby establishing a much higher degree of pressure on the arterial side of the capillaries than could possibly be produced if the outflow were not restricted at all. Furthermore, as the arterioles are capable of actively varying their calibre, this resistance may be augmented or diminished at any time, so that smaller or larger quantities of arterial blood may be allowed to escape into the capillaries and veins.

These changes in the peripheral resistance may be imitated with the help of the accompanying schema (Fig. 184) by equipping the horizontal tube with a stopcock possessing the same diameter as the main tube. If the latter is widely open, the pressure shows a gradual decline in the direction from the reservoir to the outlet.

FIG. 184.—A STOPCOCK IS INSERTED AT THE MIDDLE OF THE OUTFLOW TUBE IN ILLUSTRATION OF THE RESISTANCE FURNISHED BY THE CAPILLARIES.

Its partial closure, however, interposes a high resistance, in consequence of which the fluid accumulates between this point and the reservoir, while it declines on the side toward the outlet (Fig. 184). Concurrently, the lateral pressure exhibits a decided increase in the central section of this tube, and a fall in its distal portion. In our circulatory system changes of this kind are brought about by the contraction of the smooth muscle cells situated in the walls of the arterioles. The constriction of the lumen of these tubules increases the resistance placed in the path of the arterial blood, and prevents its free escape into the capillaries and veins.

The influence which the peripheral resistance is capable of exerting upon the flow of the blood, may be illustrated in a very convincing manner by connecting a piece of elastic band-tubing with an ordinary valved syringe. The outlet of this elastic tube should be diminished somewhat by equipping it with a narrow piece of glass tubing. If the syringe is now dipped in water and is compressed at frequent intervals, the band-tubing is distended by each influx of water, but collapses as soon as this central force ceases and allows all the water to escape through the outlet. The flow is then intermittent. If the syringe is now compressed at shorter intervals, the tubing remains more fully distended and the flow becomes remittent and finally constant. At this time the entire stretch of

tubing is under the greatest possible elastic tension and subjects the fluid within to the steady pressure of its recoiling walls. Each compression of the syringe increases the pressure slightly, while during the interims it is somewhat decreased owing to the continuous escape of fluid. It is to be emphasized, however, that this system must always be kept in a hyperfilled condition, otherwise the flow cannot remain constant.

FIG. 185.—SIMPLE SCHEMA TO ILLUSTRATE THE FACTORS PRODUCING A CONSTANT HEAD OF PRESSURE IN THE ARTERIAL SYSTEM.

a, A syringe bulb with valves, representing the heart; *b*, glass tube with fine point representing a path with resistance alone, but no extensibility (the outflow is in spurts synchronous with the strokes of the pump); *c*, outflow with resistance and also extensible and elastic walls represented by the large rubber bag, *e*; the outflow is a steady stream due to the elastic recoil of the distended bag, *e*. (Howell.)

CHAPTER XXXI

BLOOD PRESSURE

The Factors Responsible for Blood pressure.—In order to prove that the blood flows from the arteries into the veins and thus completes the circuit of the body, Harvey placed loose ligatures upon an artery and neighboring vein and raised them gently out of the wound until their lumina became fully constricted. It was then found that the central end of the artery and the distal end of the vein were highly distended, while their other ends were collapsed. If the walls of the distended segments were then pierced with the point of a needle, the blood spurted out in fine jets, but with a much greater force from the artery than from the vein. The same observation was made during capillary bleeding, because the blood oozes from these opened blood-vessels in small droplets which presently coalesce to form a sheet-like covering over the injured area. These and other observations readily prove that the blood is held in the vascular system under a certain pressure.

The term blood pressure is often used to denote the general pressure existing in the vascular system, while at other times it is intended to indicate merely the pressure prevailing in the arterial channels. This ambiguity may easily be avoided by making specific reference to

either the arterial, capillary or venous pressure, because the blood pressure really presents definite differences in accordance with the three divisions of the vascular system.

The pressure to which the circulating blood is subjected is the product of a reaction participated in by four factors; namely by: (a) the energy of the heart, (b) the quantity of the circulating blood, (c) the elasticity of the blood-vessels, and (d) the peripheral resistance. Under ordinary conditions, this pressure displays a certain constancy, and retains a level considerably above zero throughout the circulatory system with the exception of the central veins. In addition it is to be noted that it is subject to certain minor variations which are dependent chiefly upon the action of the heart and the respiratory movements. These details will be brought out more fully by the subsequent discussion.

The Energy of the Heart.—Each ventricular systole forces a definite quantity of blood into the arteries. Assuming that the other three factors remain unchanged, it may be concluded that the pressure must rise whenever a new amount of blood is added to that already existing in these channels, and that the pressure must fall whenever the ventricles enter the state of diastole. This relationship implies that the energy of the heart must be proportional to the ventricular output and must embrace the following minor factors:

(a) The volume of the cardiac output,

(b) The frequency with which these discharges are repeated, and

(c) The force with which the blood is ejected.

The first condition is determined by the capaciousness of the cardiac chambers, or better, by the power of filling of the heart, the second by the number of the discharges occurring in a given period of time, and the third by the force with which the emptying of the ventricles is effected. Right here it should be emphasized that the energy of the heart which, as has just been stated, is only one of the factors upon which blood pressure depends, is subject to fluctuations, because the conditions previously cited, do not always act in unison, but may actually counteract each other. Thus, the volume of the different ventricular outputs may be increased owing to a greater filling power or relaxability of the cardiac musculature, without being associated with a rise

FIG. 186.—RECORD OF BLOOD-PRESSURE SHOWING THE CARDIAC AND RESPIRATORY VARIATIONS.

The time registered in seconds, serves as the abscissa.

in the blood pressure. The cause of this discrepancy most frequently lies in a lessened rate of the heart. For very similar reasons it cannot be taken for granted that a rapid heart always gives rise to a higher blood pressure, because the filling power of this organ may be decreased in a measure to compensate for the increase in the frequency. Moreover, as a diminution in the power of contraction of the cardiac muscle must be followed by a reduction in the force of ejection, the blood pressure must fall even when the frequency and the filling power of the heart remain practically unaltered. And again, while an increase in the power of contraction of the cardiac musculature generally raises the pressure, this result cannot be attained if the frequency or the filling power of this organ is diminished.

In further illustration of these complex interactions between the factors giving rise to the energy of the heart, it might be mentioned that the stimulation of the vagus nerve leads to a fall in the general blood pressure, because the ventricular outputs are either diminished in number or are stopped altogether.¹ But if a strength of current is employed which is just sufficient to cause a moderate reduction in the cardiac rate, the filling power of the organ may thereby be augmented in such a measure that the blood pressure is enabled to retain its former level. Quite similarly, the cutting of the vagi nerves most generally produces a rise in blood pressure, because the removal of the inhibitory impulses permits the heart to increase its frequency, so that the number of ventricular outputs in a unit of time becomes greater. But it also happens at times that this procedure produces no augmentation at all, because a proper relaxation of the cardiac muscle cannot be effected, owing to the high frequency of contraction. Under this condition, the heart [is quite unable to eject a greater quantity of blood. Similar compensations occur at times during the stimulation of the acceleratory nerves so that the rises in pressure ordinarily resulting from this procedure, cannot attain their full development. These variations are not mere theoretical possibilities, but are frequently observed under pathological conditions. They have been cited here somewhat at length, in order that they may be made use of in explaining some of the peculiar changes in the blood-pressure occurring in the course of cardiac diseases.

It has previously been stated that the height of the blood pressure most commonly bears a direct relationship to the cardiac energy as expressed in terms of the ventricular output. This means that an increase in the latter, is followed by a rise in the blood pressure, and *vice versa*. In the second place, we have seen that the blood pressure is the product of four different factors, namely, the energy of the heart, the total quantity of the circulating blood, the elasticity of the blood-vessels and the peripheral resistance. In view of this fact, the preceding general rule should therefore be amplified to include the provision that the other three factors must remain constant. If they do not

¹ O. Frank, *Zeitschr. für Biologie*, xxiii, 1901, 1.

remain constant, their influence upon the cardiac energy may be materially modified by the changes in the other three factors. It would lead altogether too far to give a complete analysis of these interactions and hence, it must suffice to illustrate them with the help of a single example, namely the relationship existing between the energy of the heart and the peripheral resistance. It should be stated first of all that the peripheral resistance may be increased or decreased. The former change gives rise to a lessened escape of arterial blood into the capillaries, and the latter to a more copious arterial outflow. Supposing now that the cardiac energy is augmented, we would expect to obtain a rise in the arterial blood pressure. This result, however, may be nullified by a vasodilatation, *i.e.*, by a diminution of the peripheral resistance and a greater outflow of the arterial blood. In a similar manner, it may be reasoned that a lessened ventricular discharge must lead to a fall in blood pressure. But this effect is not always obtained, because the diminution in the cardiac output may be compensated for by an increase in the peripheral resistance occasioned by a vasoconstriction. The simultaneous appearance of an increased cardiac energy and peripheral resistance would, of course, raise the blood pressure. The opposite result would be obtained after a simultaneous depression of these two factors.

The Total Quantity of the Circulating Blood.—This factor bears a direct relationship to the blood pressure, because different degrees of pressure may be established very readily by simply varying the volume of the blood, provided, of course, that the other three factors remain unchanged. Conditions of this kind invariably result in the course of hemorrhages, and during the infusion of isotonic solutions and the transfusion of blood. Under normal conditions, the vascular system possesses the power of adapting itself very quickly to different quantities of blood by (*a*) varying the size of the bloodbed, (*b*) forcing the fluid elements of the blood into the lymphatic channels, and (*c*) transferring the lymph into the bloodstream. Thus, slight losses of blood are quickly compensated for by a vasoconstrictor reaction and a transfer of lymph into the vascular channels. For this reason, a decided fall in blood pressure cannot develop under these circumstances, unless the hemorrhage has been sufficiently severe to offset this compensation. A similar reaction takes place whenever the amount of the circulating blood is increased. The blood-vessels then relax, and a certain portion of the blood seeks the lymph spaces.¹ These changes are often followed by an extra discharge of water from the body in the excretions. It is true, however, that any extraordinary increase in the amount of the circulating blood gives rise to a more decided and more permanent rise in the pressure. It need scarcely be emphasized that these alterations frequently assume a local character and remain

¹ Worm-Müller (Ber. der. sächs. Gesellsch. der Wissensch., 1873), Stolnikow (Arch. für Anat. und Physiol., 1886), and Johansson and Tigerstedt (Skand. Arch. für Physiol., ii, 1889).

confined to particular divisions of the vascular system. These local hyperemias and anemias may be neutralized by vasomotor changes and a transfer of the plasma, insuring a continuance of the normal circulatory conditions.

The Elasticity of the Blood-vessels.—This factor betrays itself by a distention of the walls of the blood-vessels whenever the pressure within them rises. This elastic play is most clearly in evidence on the arterial side and particularly in the central arteries, where we find the largest number of elastic fibers. In the more distal channels, the elastic tissue is gradually displaced by smooth muscle cells, which appear here chiefly in the form of a thick layer arranged circularly around the lumen of the vessel. Some of these cells are also arranged in a longitudinal direction and in such a way that they form a thin coat externally to the circular. The peripheral arteries and arterioles, therefore, contain practically no elastic fibers, but are made up of a heavy layer of smooth muscle tissue. This difference in the structural character of the arterial system leads us to infer that the elastic forces have full sway centrally, while peripherally the prevailing factor is muscular contraction. Hence, the aorta may be regarded as an elastic pouch, the walls of which are forced outward with every ventricular output. Directly thereafter a recoil sets in at a moment when the elastic power of the arterial wall is capable of overcoming the internal pressure. This means that they accomplish their work during the diastolic interim, and constitute therefore a most important aid to the heart, because the power generated by this organ during each systole, is immediately stored in their walls as elastic tension to be made use of during the period of cardiac rest. Inasmuch as the blood is thus held under a constant pressure, the arteries serve the same purpose as the air-bladder of a bag-pipe from which the air may be drawn in a continuous stream.

The energy of the heart, the quantity of the blood and the peripheral resistance are adjusted in such a way that the arterial system is constantly retained in a state of hyperfilling. This implies that the escape of the blood into the capillaries is regulated in such a way that it is always exceeded by the ventricular output. In this way, a definite head of pressure is established which cannot be nullified during the diastolic period of the heart. It is true, however, that the pressure is somewhat greater during the systolic inrush of blood, than during the diastolic phase of gradual emptying. The outflow must necessarily be limited, because the peripheral resistance and the frequency of the heart are so accurately balanced that more than a moderate recoil of the arterial walls cannot result. Only in case the heart ceases to beat altogether do we obtain a complete collapse of these channels, the blood then accumulating on the venous side and principally in the central veins and right side of the heart. This is the condition prevailing after death.

The preceding statement leads us to infer that the diastolic fall

in the arterial blood pressure must become the greater, the longer the interval between two successive ventricular discharges. This rule, however, is not infallible, because in many cases a fall in pressure resulting from an undue slowness of the heart, may be effectively counteracted by an increase in the peripheral resistance. A compensation of this kind takes place very frequently, but naturally, it cannot overcome the dynamical disturbances produced by an excessively infrequent heart.

The elastic power of the vascular system lessens the work of the cardiac musculature very materially, because it insures a constancy of flow without necessitating an extra expenditure of energy on the part of the heart. As each cardiac output is accommodated in the arteries, their walls are forced outward. In this way, a large part of the work of the heart is converted into potential energy in the form of elastic tension which is utilized later on during the diastolic interim, and hence, the work of this organ is actually distributed over more than twice the time actually consumed in its muscular contraction. This enables the heart to obtain the rest required for its anabolism. The importance of the elasticity is also elucidated by the fact that a rigid vascular system immediately converts the otherwise constant flow into one possessing remittent and intermittent qualities. Each systole then gives rise to a quick onrush of blood which is soon followed by a slowing and a cessation of the flow. Very high and very low pressures are then obtained alternately.

The property of elasticity is possessed in a slight measure by all types of cells and not only by those composing the elastic tissues. For this reason, it cannot be said to be wholly lacking in other segments of the vascular system, although we have just seen that it becomes of greatest dynamical importance in the central arteries. The structure of the capillaries is such that varying quantities of arterial blood can readily be accommodated in them by simply changing the size of their lumen. These perfectly passive changes are made possible by the fact that they are distensible, although their elastic power is insignificant. In this connection, mention should also be made of the claim of Stricker and others,¹ that the capillary lining cells possess contractile qualities which betray themselves in active variations of their thickness at the sites of the different nuclei. The evidence so far presented in favor of this view, does not seem sufficiently conclusive to warrant further discussion of this subject. Somewhat different conditions are met with in the veins. Here the elasticity again plays a more important part, because these channels are large and are structurally in a position to oppose the pressure by a very moderate recoil. It is to be noted especially, however, that the size of the venous bloodbed is very largely dependent upon the quantity of the blood transferred to them by the arteries. They themselves cannot vary their caliber in an active way by vasomotor activity.

¹ *Berichte, Akad. der Wissensch., Wien, 1865.*

The early determinations of the elasticity of the blood-vessels, were made upon excised segments which were suspended from a hook and loaded with different weights. In as much as the curve obtained by this method resembled a hyperbole, the conclusion was drawn that the coefficient of the elasticity does not possess a constant value but increases with the distention. It seems, however, that the degree of distensibility obtained under this condition, is not comparable

FIG. 187.—MAREY'S ARRANGEMENT FOR TESTING THE ELASTIC POWER OF BLOOD-VESSELS.

The artery (*A*) is suspended in a glass tube filled with saline solution (*T*). Its ends are closed with discs of rubber and its lumen connected with a pressure bulb (*B*). The meniscus of the saline solution *M* in tube *C* indicates the degree of distention of the artery.

to the distensibility produced by an internal pressure, but merely gives us an idea regarding the compactness or strength of the blood-vessels. Marey¹ sought to establish more perfect experimental conditions by placing segments of arteries in plethysmographs and by subjecting their walls to a steady internal pressure. This end he attained by connecting the lumen of the segment with a bottle filled with saline solution which he could raise to a certain level above the preparation. Roy² and others state that a steadily rising pressure leads to a gradual increase in the caliber of the blood-vessel, but a limit is soon reached beyond which the distention diminishes very rapidly. In rabbits the normal distensibility is reached with a pressure of 70 mm. Hg, in dogs at 75 to 125 mm. Hg, and in the ox at 100 to 150 mm. Hg. A much higher pressure is required to cause a normal artery to rupture. In accordance with the determinations of Gréhan and Quinquaud,³ the carotid artery of the dog can withstand an internal pressure of 600 mm. Hg, while the lowest pressure necessary to burst the carotid artery of man amounts to 1.29 m. Hg. As the smaller arteries are even stronger than the larger ones and as the arterial pressure seldom rises above 150 mm. Hg, the margin of safety is more than ample.

It is also of interest to note that the optimum degree of movability of the vessel wall is had at a pressure most closely approaching the normal. At this time the most perfect elastic play is obtained. If the pressure is raised much beyond this point, the distensibility becomes less and less. Supposing, therefore, that the quantity of the circulating blood is increased, the power of the vascular system to accommodate

¹ Trav. de Lab., iv, 1880, 253.

² Jour. of Physiol., iii, 1881, 125; also see: Zwaardemaker (Nederl. Tijdschr. voor Jencesk., xxiv, 1888, 61), and Frank (Ann. der Physik., 1906).

³ Jour. de l'anat. et de la Physiol., xxvi, 1885.

this extra amount of blood must become the less, the higher the pressure already established. Concurrently, it may be reasoned that the energy of the heart may be most seriously impaired by forcing it to increase its activity at a time when the tension in the vascular system is high, because the vascular channels cannot then yield so readily to the internal pressure. The veins attain their maximal cubic distention at much lower pressures than the arteries, and their extensibility is much less. They are more easily torn when manipulated, but are more yielding than the arteries. This may well be so, because the pressures which they are called upon to withstand, scarcely exceed 20 mm. Hg even under pathological conditions.

The Peripheral Resistance.—This factor serves as an expression of the size of the "blood-gate" at the arteriocapillary junction. It may be inferred that the resistance placed in the path of the arterial blood, must become the less the larger this orifice. The friction which is responsible for the production of this resistance, is composed in reality of two types of frictions which may be designated respectively as the "external" and the "internal." The former is produced by the blood as a whole as it rubs against the internal surface of the vessel wall and the latter, by the bumping together of the different constituents of the blood. The term viscosity is usually applied to this intermolecular friction. It is evident that the hindrance placed in the path of the arterial blood, must increase whenever the "blood-gate" is made smaller and decrease whenever it is made larger. In the first instance, the arterial influx into the capillaries is diminished, and in the second increased. Supposing, therefore, that the other three factors remain the same, the first change must lead to a rise and the second, to a fall in the arterial pressure.

Special emphasis has been placed upon the conditions existing at the arteriocapillary junction, because the distalmost branches of the arterial system are equipped with especially powerful rings of smooth muscle cells, which enable them to influence the blood stream most decisively. This statement, however, is not meant to imply that the peripheral resistance is formed in the arterioles and not in the capillaries. A deduction of this kind could not possibly be correct, because it is a well-known fact that no segment of the vascular system produces a greater amount of friction than the capillaries. This must be so, because the column of blood is divided by them into the finest possible streams, many of which are no broader than the diameter of a single red cell. Although generators of the peripheral resistance, it is evident that the capillaries as such are quite unable to vary this resistance, because they are not in possession of an active means for influencing the blood-stream. This function is relegated to the arterioles which, as we have just seen, act as powerful sphincters, permitting larger and smaller quantities of arterial blood to escape. Consequently, the state of filling of the capillaries is determined very largely by the arterioles. In view of their decided vasomotor qualities, it

may also be concluded that they are the chief factor regulating the peripheral resistance.

Reference has repeatedly been made to the close functional relationship existing between the peripheral resistance and the energy of the heart. Thus, it has been said that a high blood pressure resulting from vasoconstriction, is commonly associated with a decrease in the frequency of the heart, and *vice versa*. Although not wishing to over-emphasize this reflex compensation, the foregoing facts will go far to show that the blood pressure is more closely dependent upon the interaction of the two factors just mentioned than upon the quantity of the circulating blood or the elasticity of the blood-vessels. No doubt, the former are subject to more frequent changes than the latter, *i.e.*, under normal conditions the quantity of the blood and the elasticity remain the same for much longer periods of time.

THE DIRECT AND INDIRECT METHODS OF RECORDING BLOOD PRESSURE

Methods for Determining the Arterial Blood Pressure.—The procedures employed to ascertain the pressures in the different parts of the

FIG. 188.—DIAGRAM ILLUSTRATING THE INDIRECT METHOD OF MEASURING BLOOD-PRESSURE.

A, arm surrounded by a flat rubber pouch, *R*; by means of a rubber bulb, *B*, a pressure is set up in this system of tubing sufficient to compress the artery. This moment is indicated by the manometer (*M*).

vascular system, differ somewhat in accordance with the nature of the blood-vessel. If the *direct method* is resorted to, the vascular channel is opened and the blood brought into immediate contact with the recording instrument. If, on the other hand, the *indirect method* is employed, the blood-vessel is left intact, while the pressure existing therein is accurately balanced by a known pressure set up in an artificial system immediately adjoining it (Fig. 188). Obviously, therefore, the direct procedure is applicable only to animals and to blood-vessels of larger caliber, whereas the indirect or bloodless method may be practised upon animals as well as upon man.

The first attempt to ascertain the pressure of the blood, was made in 1732 by the Rev. Stephen Hales,¹ an English clergyman. A long

¹ Statical Essays, 1733.

copper cannula was inserted in the artery in the groin of a horse which in turn was connected with a vertical tube of glass, measuring nine feet in height and one-sixth of an inch in diameter. On removing the ligature from the artery, the blood was seen to enter the tube to a height of eight feet and three inches above the level of the left ventricle. However, it did not rise to this height at once, but gradually, and finally exhibited small oscillatory fluctuations.

This single vertical tube was displaced later on by a U-shaped tube, a further reduction in its length being made possible by filling it with mercury, because this element possesses a specific gravity 13.5 greater than that of water. Ludwig finally equipped the distal limb of the mercury column of these manometers with a float and slender vertical rod to which he attached a writing point. This arrangement enabled him to record the excursions of the mercury upon the paper of a kymograph (Fig. 149). In recent years use has also been made of various types of membrane-manometers, in which the intravascular pressure is counter-balanced by the elastic force of a rubber membrane. The displacements of this membrane can be accurately recorded by permitting it to act against a writing lever, or by permitting it to reflect a beam of light from a delicate mirror fastened to its surface.

For obvious reasons the direct method can only be applied to arteries and veins which are sufficiently large to allow the introduction of a cannula. On the arterial side, the pressure is measured most conveniently in the carotid and femoral arteries, the former blood-vessel being used most frequently, because it is more accessible and in closer proximity to the center of the circulatory system. In either case, it should be remembered that we are not determining the pressure in this particular vessel, but in the one situated centrally to it. To illustrate, the carotid artery leaves the aorta almost at right angles and plays, therefore, the same rôle as the free end of a T-tube, *i.e.*, it permits the pressure which is exerted in a radial direction upon the internal surface of the wall of the aorta to be propagated directly outward into the manometer (Fig. 189). It must be clear, therefore, that the pressure prevailing in the carotid artery itself can only be ascertained if this vessel is connected with the recording instrument either by means of a T-tube, or by means of a straight cannula inserted into one of its branches. This purpose may be served by the arteria thyroidea, because the lateral carotid pressure is propagated through this blood-vessel directly into the manometer (Fig. 189, II). In this connection attention should also be called to the fact that the distal stump of an artery is not necessarily without pressure, because in most cases anastomoses are present which permit at least a slight quantity of blood to enter this channel in an indirect way.

In order to ascertain the venous pressure, it is necessary to insert a T-tube, the free end of which is connected either with a U-shaped manometer filled with normal saline solution, or with a membrane manometer possessing the least possible resistance. The oscillations of the column of saline solution may be registered by placing a bell-shaped float and writing needle upon its distal limb. This modification in the method of registration is made necessary by the fact that the

FIG. 189.—DIAGRAM TO SHOW THAT A MANOMETER CONNECTED WITH THE CAROTID ARTERY MEASURES THE LATERAL PRESSURE IN THE AORTA.

pressure throughout the venous system is very low and cannot therefore support a column of mercury of adequate height nor deviate a membrane possessing slight elastic powers. Furthermore, the venous pressure cannot be measured by connecting the manometer with the peripheral or central end of the vein, because the blocking of the distal stump of the vein would give rise to a venous stagnation which would be indicative of the pressure prevailing in the corresponding arterial supply tubes. Quite similarly, the use of the central stump would expose the manometer to the pressure existing in the more central vein.

Having inserted a suitable cannula in the blood-vessel, the entire tubing between it and the manometer is filled with a solution tending to prevent the coagulation of the blood. A saturated solution of sodium carbonate or bicarbonate, a 5 per cent. solution of sodium citrate or a 25 per cent. solution of magnesium sulphate may be used for this purpose. A device which often saves much time is to connect the manometer with a reservoir containing one or the other of these solutions, so that the connecting tubes may be flushed out whenever they become blocked by coagula. On the venous side, a 0.7 per cent. solution of sodium chlorid should be employed, because as the pressure encountered in these channels is low, and may even fall below zero, a part of the fluid in the connecting tube may be drawn into the circulation and, unless non-toxic, may produce depressive effects. In some cases it may be necessary to render the blood as a whole non-coagulable, which end may be accomplished by the injection of a solution of peptone or of an extract of leeches (hirudin).

On removing the clamp previously placed upon the artery, the blood will be seen to enter the connecting tube and to displace the column of mercury outward until the weight of the latter exactly counterbalances the blood pressure. As soon as an equilibrium between these two opposing forces has been established, the mercury undergoes a series of rhythmic fluctuations, the smaller ones of which are dependent upon the contractions of the heart and the larger ones upon the respiratory movements. The former are known as the cardiac and the latter as the respiratory variations in the arterial blood pressure. Both must be sharply differentiated from oscillations of a similar kind which appear in the central veins and are designated as the cardiac and respiratory variations in venous pressure. Moreover, if the experimental conditions are especially favorable, a third type of variation frequently appears in the arteries which is of much longer duration than the others and is known as the Traube-Hering curve. The character and cause of these changes will be considered more fully in a subsequent chapter.

It has been pointed out above that the mercury is quite unable to follow quick changes in pressure with accuracy. On this account, a membrane manometer should be used whenever it is desired to depict the character of the individual pulsations. A mercury manometer, on the other hand, should be employed whenever it is intended merely to obtain a general picture of the height of the pressure. Special directions for the use of these instruments have been given previously (page 293).

The Arterial Pressure in Different Animals and Arteries.—The direct method has been applied to man in a few isolated cases, when it became necessary in the course of operations to divide certain peripheral blood-vessels. For the femoral and brachial arteries¹ the average value of 120 mm. Hg has been found and for the tibial the value of 80–90 mm. Hg. The pressures obtained under the most favorable conditions in other animals have been compiled by Volkmann and Nikolai as follows:

¹ Faivre, *Gazette méd. de Paris*, 1856, and Albert, *Med. Jahrb.*, Wien, 1883.

Horse.....	180 mm. Hg
Calf.....	160 mm. Hg
Sheep.....	160 mm. Hg
Dog.....	140 mm. Hg
Goat.....	130 mm. Hg
Cat.....	110 mm. Hg
Rabbit.....	100 mm. Hg
Guinea-pig.....	85 mm. Hg

As the fluctuations even among animals of the same species are very considerable, it is not apparent that the size of the animal bears a direct relationship to the pressure. It is also noted that the pressures among animals of different species vary so widely that they overlap. In spite of this divergency, however, there seems to be a definite tendency on the part of animals of the same group to preserve a certain height of blood pressure. The cold-blooded animals show much lower values than the mammals. The following table may be of interest:

Cephalopods.....	25-80 mm. Hg ¹
Fishes (torpedo).....	25 mm. Hg ²
Amphibia:	
Grassfrog.....	29-40 mm. Hg ³
Bullfrog.....	22-26 mm. Hg ⁴
Reptilia:	
Crocodile.....	30-50 mm. Hg ³
Turtles.....	25-35 mm. Hg ⁵

Concerning the arterial pressure it may be stated that it diminishes gradually in the direction from the heart toward the periphery, but the decrease is slight, because the pressure in the distalmost arteries is only a few millimeters below that prevailing in the aorta. This fact implies that the blood does not encounter a considerable resistance during its journey to the arterioles. Volkmann, for example, found the pressure in the carotid arteries of two calves to be 116.3 and 165.5 mm. Hg, respectively, while the pressure in the metatarsal arteries amounted as yet to 89.3 and 146.0 mm. Hg. For the dog Fick⁶ gives the values of 176 mm. Hg for the aorta and 132 mm. Hg for the tibial artery. According to Burton-Opitz,⁷ the difference in pressure between the femoral and hepatic arteries of the dog amounts to 4.4 mm. Hg, and between the former and the more distal arteria gastroduodenalis to 10 mm. Hg. The fact that the original pressure is used up much more rapidly in the distalmost branches of the arterial system is indicated by the observations of v. Frey,⁸ who has furnished the following data:

¹ Fuchs, Pflüger's Archiv, 60, 1895, 173.

² Schönlein, Bull. scient. de la France, xxvi.

³ Hofmeister, Pflüger's Archiv, 44, 1889.

⁴ Burton-Opitz, Am. Jour. of Physiol., vii, 1902, 243.

⁵ Edwards, *ibid.*, xxxiii, 1914, 229.

⁶ Festschr. zur Iten Säcularf. der Univ. Würzburg, i, 1882.

⁷ Pflüger's Archiv, cxlvi, 1912, 344.

⁸ Festschr. für B. Schmidt, Leipzig, 1896.

Radial artery at wrist.....	150-160 mm. Hg
Radial artery at base of thumb.....	120-130 mm. Hg
Radial artery at last phalanx.....	100-110 mm. Hg

In this connection the following determinations of the mean blood pressure in dogs, made by Dawson,¹ may be of interest:

Carotid, brachiocephalic, superior mesenteric and renal arteries.....	123 mm. Hg
Inferior mesenteric artery.....	119 mm. Hg
Iliac, femoral, saphenous and brachial arteries.....	118 mm. Hg
Arteries of the circle of Willis.....	104 mm. Hg

The Indirect Method of Recording the Arterial Blood Pressure.

The Method of Palpation.—The principle upon which the indirect method is based is simple, and has really been employed for centuries in palpating the pulse. Two or three fingers are usually used for this purpose, the artery being compressed with the central finger until the pulsations can no longer be felt with the more distal one. The force required to occlude the artery serves as the measure of the pressure existing within it.

The indirect method consists in establishing a known outside pressure which exactly balances the pressure in the blood-vessel. The first instrument of this type was constructed by Vierordt² who attempted to measure the degree of pressure necessary to obliterate an artery by attaching a pelotte to the receiving lever of a sphygmograph. A distinct advance was made in 1876 by v. Basch³ who employed a glass tube which was closed at one end by a rubber membrane and was then filled with water. Its free end was joined with a mercury manometer so that the pressure required to occlude the artery could be accurately registered. In 1883, v. Basch advised the use of a metal capsule (C) which was closed by a rubber membrane and equipped with a metal spring and indicator (M). This principle was subsequently made use of in the construction of the dynamometer of Hill and Bernard⁴ and the sphygmometer of Oliver.⁵ At about this time the experiments of Marey led to the invention of the plethysmograph, an instrument which was made use of by him as well as by Hürthle⁶ and Mosso⁷ for the compression of the artery.

FIG. 190.—VON BASCH SPHYGMOMANOMETER.

C, metal capsule and rubber pouch for occluding artery; M, tonometer for registration of pressure which is necessary to occlude the artery.

¹ Am. Jour. of Physiol., xv, 1905, 244.

² Lehre vom Arterienpuls, 1855.

³ Zeitschr. für klin. Med., ii, 1883, 79.

⁴ Jour. of Physiol., xxiii, 1898, 4.

⁵ Ibid., xxii, 1897, 51.

⁶ Deutsche med. Wochenschr., 1896.

⁷ Zentralbl. für Physiol., x, 1896.

A very simple sphygmomanometer has been devised by Riva-Rocci.¹ A rubber pouch measuring 5 cm. in width and possessing a length sufficient to encircle the arm, is connected with a mercury reservoir and a pressure bulb. This rubber bag is protected upon its outside by a leather or canvas cuff which is tightened until it fits the arm snugly. The arm is placed in an easy position at the level of the heart, and consequently, no corrections need be made for the hydrostatic effects. If the pouch is now inflated, the pressure in this system rises until the tissues around the brachial artery are compressed in such a degree that the lumen of this blood-vessel is obliterated. This moment is clearly marked by the disappearance of the pulsations in the radial artery, while the pressure necessary to accomplish this end is registered by the manometer of the mercury reservoir. The best procedure to be followed is this: The cuff having been properly adjusted, the fingers of the left hand are placed upon the radial artery at

FIG. 191.—RIVA-ROCCI'S SPHYGMOMANOMETER. (From Janeway's "*Clinical Study of Blood-pressure*," D. Appleton and Co., Publishers.)

the wrist, while the right hand is employed to inflate the rubber pouch. The pressure is read at the very moment when the radial pulse disappears. In quite the same way, the pressure is again noted when the pulse reappears during the gradual deflation of the pouch. The principle involved in this procedure is obvious. When the outside pressure just barely overcomes the intravascular pressure, as is indicated by the loss of the radial pulse, the former may correctly be taken as a measure of the latter. Naturally, this procedure does not permit of definite conclusions being drawn regarding the mean blood pressure, but indicates solely the maximum or systolic blood pressure, *i.e.*, the moment when the peaks of the individual pulse waves are just capable of overcoming the outside pressure.

¹ Gaz. med. di. Torino, 1896.

The Method of Auscultation.—The moment of the disappearance and reappearance of the pulse may also be determined by means of auscultation, because, as Marey has noted, the constriction of an artery gives rise to noises (*bruit de souffle*) which are heard best distally to and in the immediate vicinity of the constriction. Thus, if a stethoscope is applied over the brachial artery below the border of the arm-piece,¹ the gradual deflation finally gives rise to a sharp blowing sound which presently becomes fuller and then disappears altogether. The first occurrence of this sound indicates the systolic height of the blood pressure, while the moment at which the sound becomes muffled shortly before its complete disappearance, corresponds to its diastolic value. The mean pressure can only be obtained in an approximate way with the help of these two extremes.

The Graphic Method.—The determination of the blood pressure may also be attempted in accordance with the principle that the arterial wall executes its greatest movements at a time when the intravascular pressure is accurately balanced by the outside pressure. This fact to which attention was first called by Marey, has been proven experimentally by Mosso upon excised segments of arteries. The idea is to oppose the intravascular pressure by an outside pressure which, being equal to that within, permits the most perfect elastic play of the arterial walls. Thus, if the hand is placed in a receptacle filled with mercury, the pulse is felt either at the base of the thumb or along the fingers. In accordance with von Frey,² the pressure prevailing in the blood-vessels of the hand may be obtained by determining in millimeters the depth to which it must be pushed into the mercury in order to produce this subjective phenomenon. In a similar way, it is possible to register the arterial pressure upon the paper of a kymograph by simply connecting a recording tambour with the cuff of a sphygmomanometer or with the free end of its mercurial indicator. During the complete compression of the brachial artery, the pulsations so registered retain a small amplitude, because they are simply transmitted from the central end of this blood-vessel. When however, the outside pressure is lowered step by step, their size is gradually increased up to the time when the diastolic mean value of the blood pressure has been reached. Subsequent to this point the conspicuousness of these oscillations is again diminished. In this way, the moment may be accurately determined at which the outside or extravascular pressure precisely equals the intravascular pressure. Quite similarly, if the pressure is gradually increased, the beginning of the large oscillations indicates the diastolic minimum.

This procedure must be followed if measurements are undertaken

¹ In accordance with Janowski, *Münchener med. Wochenschr*, 1907, the auscultation method was first employed by Karotkow in 1895. Also see: Strassburger, *D. Archiv für klin. Med.*, 1907, 459, and Fellner, *Verhandl., Kongr. für inn. Med.*, 1907.

² *Festschrift für B. Schmidt*, Leipzig, 1896, 79.

with the sphygmomanometers devised by Erlanger¹ and Münzer² or with the sphygmoscope of Bing,³ or the oscillometer of Widmer.⁴ It is true, however, that the greatest number of instruments of this kind are modifications of the Riva-Rocci apparatus⁵ described previously. The fundamental principle has remained the same in all cases and only insignificant changes have been made. Thus, it has been shown by direct measurements, that a narrow arm-piece gives somewhat lower values, and hence, a much broader one, measuring 12 cm. in width; is now most commonly employed. In addition, the original mercury-

FIG. 192.—JANEWAY'S SPHYGMOMANOMETER.

A, folding U tube; B, arm cuff; C, pressure bulb; D and E, needle-valve for release of pressure; F, cork for closing end of mercury tube.

reservoir has been displaced in several of them by a modern mercury manometer to which a more convenient and patent form has been given so that it can be carried from place to place without spilling the mercury. An ordinary valved rubber bulb may be used for the inflation and deflation of the cuff. By using the metal tonometer devised by v. Basch, as a sample, certain instruments have recently been con-

¹ Am. Jour. of Physiol., Proc. xxii, 1902, also *ibid.*, x, 1904.

² Münchener med. Wochenschr., 1907, 1357.

³ Berliner klin. Wochenschr., 1907, 690.

⁴ Vaquez, Compt. rend., lxvi, and Paris médicale, 1911.

⁵ Gärtner, Wiener med. Wochenschr., xxxi, 1899, and Martin, Münchener med. Wochenschr., xxiv, 1903.

structed in which a metal spring¹ is employed instead of the mercury manometer. These so-called sphygmotonometers possess the advantage of being convenient to handle, although they must be calibrated repeatedly to make sure that the tension of the spring has not changed.

The Factors Influencing the Arterial Pressure.—As far as the influence of *age* is concerned, it has been well substantiated that the arterial blood pressure increases constantly until the normal mean is reached in adult life. In later years and old age, it again increases owing to the fact that the elasticity of the vascular tissue diminishes steadily at this time in consequence of retrogressive changes. These facts are fully illustrated by the succeeding table in which values furnished by Cook and Briggs,² Shaw,³ McCurdy and Thayer⁴ have been included:

First few months.....	70-75 mm. Hg
1-2 years.....	80-90 mm. Hg
2-3 years.....	90-100 mm. Hg
3-10 years.....	95-115 mm. Hg
10-15 years.....	100-115 mm. Hg
15-20 years.....	105-128 mm. Hg
20-30 years.....	135 mm. Hg
30-40 years.....	140 mm. Hg
40-50 years.....	142 mm. Hg
50-60 years.....	154 mm. Hg
60-70 years.....	180 mm. Hg

Janeway⁵ considers 150 mm. Hg as the upper limit in normal adults, while a systolic pressure of 60-75 mm. Hg is generally regarded as dangerously low, although a pressure of 30-40 mm. Hg is sometimes observed during operations. The average normal systolic pressure amounts to 135-145 mm. Hg; women generally showing a somewhat lower pressure than men. Persons with sedentary habits usually exhibit a pressure between 120 and 125 mm. Hg. The diastolic pressure most frequently retains a value about 35-40 mm. Hg below that of the systolic.⁶ If the pressure persists for longer periods of time at 180-200 mm. Hg, and over, a condition of hypertension is said to exist. Quite similarly, persistent low pressures indicate a state of hypotension. Both conditions generally possess pathological causes.

The pressure is lowest during the first hours of *sleep*, and rises gradually until the time of awakening, when it increases rather suddenly to a level somewhat higher than that retained before retiring.⁷ During the day the blood pressure shows considerable variations which

¹ von Recklinghausen, *Archiv für exp. Pathol.*, lv, 1906, 375.

² Johns Hopkins Univ. Report, xi, 1903, 451.

³ Albany Med. Jour., xxi, 1900, 88.

⁴ Am. Jour. Med. Sciences, cxxvii, 1904, 391.

⁵ Clin. Study of Blood Pressure, New York, 1904.

⁶ Hirschfelder, *Diseases of the Heart and Aorta*, Lippincott, Philadelphia, 1913, and Faught, *Blood Pressure*, Saunders Co., 1916.

⁷ Brush and Fayerweather, *Am. Jour. of Physiol.*, v, 1901, 199.

must be attributed to diverse external and internal influences. Fluctuations of 50 to 60 mm. Hg are not uncommon. *Meals* possess an augmentor effect, in spite of the fact that the portal blood-vessels receive large quantities of blood during the periods of digestion.¹ Janeway's charts show a rise of 5 mm. Hg in the systolic and a fall of 5 mm. Hg in the diastolic pressure after the midday and evening meals. To this augmentor effect, as well as to the sudden reflex vasoconstrictor reaction, must be attributed the peculiar cerebral symptoms which are frequently experienced after too hearty a meal. Apoplectic seizures are prone to occur under these circumstances, provided, of course, that the arteries have been rendered brittle by calcareous infiltration. Deep and forced *breathing* increases the pressure. It is decreased during *menstruation*,² but rises during *pregnancy*,³ especially during its later stages, and shows a most decided increase during *labor* in consequence of the pronounced sensory stimulations and musculo-motor efforts. *Baths* at the temperature of the body have no marked effect, but cold baths (30–35° C.) produce a rise in the systolic pressure. Hot baths (40° C. and over) generally possess a similar effect on account of the resulting increase in the frequency of the heart.⁴ Water containing carbon dioxid, acts augmentatively, but only if the cardiac energy has not been diminished.

As far as the influence of *muscular exercise* is concerned, the more recent determinations which have been made with the help of the indirect method, seem to fully bear out the results obtained in horses and dogs at an earlier date by means of the direct method.⁵ Thus, Hill⁶ has shown that on moving about, the pressure rises from 10 to 20 mm. above that shown when at rest or asleep. Furthermore, the experiments of Edgecomb and Bain,⁷ Masing,⁸ Karrenstein,⁹ Lowsley,¹⁰ and others have demonstrated that the effect of muscular work depends entirely upon its severity. In all forms of it, an initial rise results, which is retained for a time if the muscular efforts have been slight, or is displaced by a fall, if the exercise has been severe or of long duration. A moderate fall in arterial pressure, however, is not an uncommon symptom of moderate muscular work.

¹ Gumprecht, Zeitschr. für klin. Med., xxxix, 1900; Jellinek, *ibid.*, xxxix, 1900; Somerfeld, Dissertation, Erlangen, 1901, and Janeway, Clin. Study of Blood Pressure, New York, 1904.

² Federn, Wien. klin. Wochenschr., xv, 1912.

³ Wiessner, Deutsch. Arch. für klin. Med., 1907, and O. Müller, Kongr. für Inn. Med., 1902.

⁴ Strasburger, Zeitschrift für klin. Med., liv, 1904, 373.

⁵ Zuntz and Hagemann, Deutsch. med. Wochenschr., 1892, and Kaufmann, Archiv de physiol., ser. 51t. 4.

⁶ Jour. of Physiol., xxii, 1898, Proc. 26.

⁷ *Ibid.*, xxiv, 1899, 48.

⁸ Deutsch. Arch. für klin. Med., lxxiv, 1902.

⁹ Zeitschr. für klin. Med., i, 1903.

¹⁰ Am. Jour. of Physiol., xxvii, 1911, 446.

While ordinary changes in *position*¹ do not affect the blood pressure very materially, extreme changes always induce static effects which the vascular system is at times unable to counteract. Thus, a change from the recumbent to the standing position always leads to a fall in blood pressure, if the tonus of the blood-vessels has been lessened in any way. This condition may be general or local, and is especially prone to involve the blood-vessels of the portal system. As these channels are concerned with the digestion and absorption of foods, they must absorb a large mass of blood, and hence, their static influence must be particularly potent at this time. The effects of vascular relaxation are counteracted in a large measure by a greater ventricular discharge, because if a person assumes the erect position, the heart beats more quickly, this increase being proportional to the fall in pressure. If, however, the relaxation is pronounced, the heart is quite unable to effect an adequate compensation and a fall in blood pressure results. Concurrently, it may be concluded that a proper tonicity of the blood-vessels suffices to retain the pressure at its normal level without that the heart need increase its energy. In fact, a person whose vascular system is tonically set, most frequently shows a slight rise on assuming the erect position, because the heart nevertheless tends to increase its frequency by at least a few beats.

These facts have been employed by Crampton² in obtaining an *index of condition*. A large number of determinations of the blood pressure in normal individuals have been compiled in such a way that their state of physical fitness may be deduced directly from these figures. This is made possible by arranging these values in series in accordance with the alterations in the height of the blood pressure and the frequency of the heart which resulted when these persons changed their position from the recumbent to the upright. In accordance with these determinations, a person is said to be in a good physical condition if, on assuming the erect position, his systolic pressure diminishes by no more than 12 nor increases by more than 18 mm. Hg. Besides, this change must leave the diastolic pressure unchanged, or must not increase it by more than 18 mm. Hg. Quite similarly, the heart must at this time either retain its previous rate or increase its frequency by no more than 40 beats. Greater variations than these are regarded as proving that the vascular system is relaxed and that, therefore, the person is in a poor physical condition. While this test possesses a sound dynamical basis, the results obtained should be accepted with great reserve and should not be applied with undue strictness to all persons.

It should be mentioned that tests of physical fitness have also been devised by Graupner,³ and Katzenstein.⁴ The former endeavored to test the functional capacity of the heart by noting the influence of a measured amount of muscular work upon the blood pressure and pulse rate, and the latter, by determining the response of the heart to compression of both iliac arteries. Barach⁵ has sought to determine the tonic condition of the circulatory system by multiplying the systolic

¹ Shapiro, Med. Jahrb. der K. K. Gesellsch. d. Ärzte, 1882; Erlanger and Hooker, Johns Hopkins Hosp. Rep., xii, 1904, and Bröcking, Zeitschr. für Exp. Path., ix, 1907.

² Med. News, 1905.

³ Berliner klin. Wochenschr., 1902.

⁴ Ibid., 1907.

⁵ Jour. Am. Med. Assoc., 1914.

and diastolic pressures by the pulse rate. When added to one another, the values so obtained give the so-called S. D. R. index, for example:

$$\text{Systolic pressure } 120 \text{ mm. Hg} \times 72 = 8,640 \text{ mm. Hg}$$

$$\text{Diastolic pressure } 70 \text{ mm. Hg} \times 72 = 5,040 \text{ mm. Hg}$$

$$190 \text{ mm. Hg} \times 72 = 13,680 \text{ mm. Hg}$$

By combining in this way the pressure with the cardiac frequency, it is possible to obtain an estimate of the vascular energy for longer periods of time. The highest S. D. R. index which has been observed in normal persons is close to 20,000. Thus, a person with a total energy index of 30,000 may be said to show a 50 per cent. increase, and so on. The lower limit seems to lie at about the figure 12,000. The efficiency test described by Barringer¹ consists in determining the cardiac rate and blood-pressure before and after a graded exercise which may be determined in foot-pounds.

The Venous Blood Pressure.—It has been stated above that the venous pressure may be determined in any vein of convenient size and location by connecting it by means of a T-tube with a U-shaped manometer containing normal saline solution. In this way, the lateral pressure is obtained which prevails in this vein at the point of insertion of the tube. By simultaneously registering the pressure in different veins of the dog, Burton-Opitz² has obtained the following average values:

Saphenous vein (left).....	7.42 mm. Hg
Femoral vein (left).....	5.39 mm. Hg
Femoral vein (right).....	5.42 mm. Hg
Facial vein (left).....	5.12 mm. Hg
Brachial vein (right).....	3.90 mm. Hg
Renal vein.....	10.9 mm. Hg
Mesenteric vein.....	14.7 mm. Hg
Splenic vein.....	10.1 mm. Hg
Portal vein.....	8.9 mm. Hg
External jugular vein (left).....	0.52 mm. Hg
External jugular vein (right).....	-0.08 mm. Hg
Superior cava (per. portion).....	-1.38 mm. Hg
Superior cava (centr. portion).....	-2.96 mm. Hg
Inferior cava at hep. vein.....	0.00 mm. Hg

This compilation shows that the pressure decreases gradually from the periphery to the center at the rate of about 1 mm. Hg for every 35 mm. of distance. The zero-line is reached in close proximity to the chest. Centrally to this point, the pressure becomes negative and eventually attains its lowest value in the auricular portion of the heart, namely -10 to -15 mm. Hg. As the pressure in the peripheral veins is only 10 to 15 mm. Hg, the total fall in the venous system amounts to no more than 30 mm. Hg. It should also be remembered that this fall is had only because the soft walls of the venous channels are constantly exposed to the elastic pull of the lungs which becomes greatest during inspiration. This can readily be proved, because

¹ Arch. of Int. Med., March, 1916.

² Am. Jour. of Physiol., ix, 1903; also Pflüger's Archiv, cxxix, 1908.

if the chest is opened, the pressure in the central veins rises immediately to above zero with a corresponding elevation of the pressure from here outward. Hence; it may be concluded that this negative venous pressure is dependent upon the elastic recoil of the lungs.

Under normal conditions, the area of negative venous pressure begins at about the junction of the hepatic vein with the inferior cava, and at the point where the external jugular vein passes deep into the supraclavicular fossa. The so-called "danger line" of the

FIG. 193.—DIAGRAM TO PRESSURE THROUGHOUT THE VASCULAR SYSTEM.

Z, abscissa or zero-line; P, curve of pressure (A) in arteries (C) in capillaries and (V) in veins. The greatest fall in pressure occurs in the capillaries in which the resistance is greatest.

surgeon corresponds to this line of zero pressure, because it has always been thought that an injury to a vein centrally to this point, must inevitably lead to an entrance of air into the vascular system and a frothing of the blood by the cardiac valves. This danger, however, is not so imminent as might be supposed, because the walls of the veins yield easily and, as they are not firmly attached to the surrounding tissues, collapse very readily, thereby preventing the ingress of air. Moreover, while dangerous on account of the possible occurrence of emboli, small quantities of air are frequently gotten rid of by absorption.

FIG. 194.—SMALL RUBBER CAPSULE USED FOR OBLITERATION OF VEIN.

The principle of the indirect method of measuring venous blood pressure is precisely the same as that made use of in determining the arterial pressure. An outside pressure which can be accurately measured, is brought to bear upon a superficial vein until its central stump becomes empty. As the venous pressure is low, a water manometer is employed as the indicator in conjunction with an ordinary pressure bulb. In accordance with v. Recklinghausen,¹ the obliteration of the vein is accomplished by means of a small capsule of thin rubber (Fig. 194) which communicates with a manometer, and is held in place upon the skin by a flat box made of glass or wood. Hooker² employs a small glass chamber which is fastened to the skin in the region of the vein by a film of collodion solution.

¹ Archiv für Exp. Path. und Pharm., lv, 1906.

² Am. Jour. of Physiol., lxxiii, 1914, Proc. 27.

The compression of the vein can also be accomplished by means of a spring manometer such as was first employed by von Frey,¹ or by means of a cuff connected with a water manometer. Frank and Reh,² for example, use two cuffs, one of which is applied to the forearm and the other to the arm. The former is inflated so as to fit snugly, but without exerting a pressure of more than 1 cm. H₂O. The arm-cuff is then inflated slowly until the pressure in the manometer connected with the lower cuff, is suddenly seen to rise. This change is taken to indicate an increase in the volume of the arm caused by the obstruction to the venous return distally to the arm cuff. When this obstruction first becomes evident, the pressure in the distal cuff must equal the venous pressure. Obviously, these determinations must either be made at the level of the heart or must be corrected for this level, because the pressure in any vein varies with its position. Thus, if the arm is allowed to hang pendant at the side, the pressure in the

FIG. 195.—METHOD OF MEASURING VENOUS BLOOD-PRESSURE.

The rubber capsule is adjusted upon the vein and is covered with a glass plate or small box glued to the surface with collodion. The capsule is connected with a manometer and pressure-bulb. (*v. Recklinghausen.*)

veins of the hand is much greater than when it is elevated to a point above the heart.

Gärtner³ has advised the following procedure. If the arm is slowly raised, the veins of the hand collapse as soon as a certain level has been reached. If the distance between this level and that of the heart at the junction of the fifth costal cartilage with the sternum is now measured, we obtain the pressure supporting the blood at the right auricle in centimeters of blood, or water, because 10 cm. of blood equal 10.6 cm. of water. Moritz and Tabora⁴ have called attention to the fact that the venous pressure corresponds to the pressure necessary to cause normal saline solution to enter the body. If the infusion is made through the median vein of the arm when placed at the level of the heart, the pressure in this vein must correspond to the height of the column of saline solution still left in the buret at the end of the injection. It is of interest to note that the values obtained with the

¹ Deutsch. Archiv für klin. Med., lxxiii, 1902.

² Zeitschr. für Exp. Path. und Therap., 1912; also see: A. A. Howell in Arch. für int. med., ix, 1912.

³ Münchener med. Wochenschr., lxxlv, 1904.

⁴ Deutsch. Archiv für klin. Med., xeviii, 1910.

aid of these indirect methods closely agree with those given previously. Thus, it has been found that the pressure in the small veins of the arm and hand amounts to 100–200 cm. H_2O .

The Capillary Blood Pressure.—Obviously, the pressure prevailing in the capillaries cannot be measured by the direct method; in fact, even the indirect procedures so far devised have given only approximate values. Thus, v. Kries¹ has made use of a thin plate of glass which he placed upon the skin and gradually weighted until the skin underneath it became pale. This method is based upon the probability that the first indication of the paling of the surface corresponds to the moment when the pressure in the capillaries is balanced by the pressure without. The latter may be expressed in centimeters of water by dividing the weight which has been placed upon the glass slide by the size of the area under compression. Roy and Graham-Brown² have attempted to determine the moment of compression of the capillaries by exposing them, while under microscopic observation, to a pressure brought to bear upon them by means of elastic capsules connected with a manometer.

FIG. 196.—
APPARATUS OF
VON KRIES FOR
MEASURING CAP-
ILLARY BLOOD-
PRESSURE.

When the arm was held at the level of the heart, the pressure in the capillaries of the fingers amounted to 24 mm. Hg. With the hand pendant at the side of the body, the pressure rose to 62 mm. Hg. In the capillaries of the ear, the pressure amounted to 20 mm. Hg and in those of the gums of a rabbit, to 33 mm. Hg. The determinations of von Recklinghausen³ have given a value of 55 mm. Hg for the small arterioles supplying the capillaries of the tips of the fingers.

While the capillary pressure must vary in different organs and tissues, it seems that its average value must lie somewhere between 40 and 50 mm. Hg. To illustrate: If the intraventricular pressure is 125 mm. Hg, it will be found that the peripheral arterial pressure amounts to about 105 mm. Hg. About 3 or 4 mm. Hg of the initial driving force are lost between the heart and the aorta and the remainder between this blood-vessel and the arterioles. Distally to these, the original driving force is used up very rapidly, the greatest reduction occurring in the capillaries proper. This cannot cause surprise, because the resistance in these channels is very great. As we have seen, the blood arrives in the distal veins under a pressure of only about 10 to 15 mm. Hg and hence, almost 100 mm. Hg of the original pressure have been used up in forcing the capillary passage. As the blood approaches the heart, the pressure becomes less and less, amounting at the cardiac vestibule to only –5 to –10 mm. Hg. Naturally, these negative values which are de-

¹ Verh. sächs. Gesellsch. der Wissensch., 1875.

² Jour. of Physiol., ii, 1879, 323.

³ Archiv für Exp. Path. und Pharmak., lv, 1907.

pendent upon the elastic pull of the lungs upon the soft walls of the central veins, serve as accessory means to augment and to conserve the initial driving force of the heart.

CHAPTER XXXII

THE PULSATORY VARIATIONS IN BLOOD PRESSURE

A. THE CARDIAC VARIATIONS IN ARTERIAL PRESSURE

The Cause of the Arterial Pulse.—Fluctuations in pressure are encountered in the arteries as well as in the veins; in fact, they are also perceptible at times in the capillaries. They possess a twofold origin, being caused either by the contractions of the heart, or by the movements of respiration. If the former, they are designated as the cardiac, and if the latter, as the respiratory variations in blood pressure. Moreover, as each group of changes makes itself felt in the arteries as well as in the veins, they are again subdivided into the cardiac variations in arterial and venous blood pressure, and into the respiratory variations in arterial and venous pressure. The principal changes due to the activity of the heart, are the so-called arterial pulse and the physiological venous pulse.

Each ventricular systole adds a certain quantity of blood to that already transferred into the arterial system by the preceding systoles. The arterial pressure increases with each ventricular discharge above that prevailing during the previous diastolic period. Furthermore, owing to the elasticity of the arterial channels, each inrush of blood causes a distention of their walls which is followed by a recoil as soon as the influx has ceased. Obviously, this elastic play serves the purpose of lessening the systolic strain upon the cardiac muscle as well as that upon the walls of the blood-vessels, because if the heart were forced to pump into a system of rigid tubes, its contractions would necessarily become labored, owing to the fact that a certain amount of blood would first have to be dislodged from the tubes before a new amount could be accommodated therein. A condition of this kind would occasion a periodic escape of venous blood to counterbalance the quantity of arterial blood forced in, and this intermittent or remittent flow would be characterized by very high systolic and very low diastolic pressures.

Contrary to this result, the distensibility of the arterial walls enables this system to accommodate the successive outputs of the heart by simply enlarging its caliber. Moreover, this process insures the least possible expenditure of energy and does not permit of the development of disturbing fluctuations in pressure and flow. In addition, the subsequent recoil of the arterial walls serves the purpose of con-

tinuing the initial driving force of the heart even during the diastolic period, so that the blood is forced to escape into the capillaries in a perfectly steady stream and not remittently. Obviously, therefore, the pressure in the arteries is increased during each systole of the heart, and, as the ventricles are emptied rather quickly (0.3 sec.), this rise must develop with a certain abruptness. The diastolic decline, on the other hand, is gradual, because the peripheral resistance is adjusted in such a way that a very copious escape of arterial blood during this period cannot result. By means of a proper adjustment of this resistance, the arterial system is constantly kept in a condition of overfilling.

The aforesaid systolic-diastolic variation in the arterial pressure forms the basis of the arterial pulse. Although primarily dependent upon the activity of the heart, its place of origin is really in the root of the aorta, whence the individual fluctuations in pressure are trans-

FIG. 197.—THE CARDIAC VARIATIONS IN THE ARTERIAL BLOOD-PRESSURE.

S, systolic pressure; D, diastolic pressure; M, average pressure. The systolic-diastolic difference constitutes the pulse-pressure. A, abscissa.

mitted throughout the arterial system in the form of successive waves. Thus, it happens constantly that the central portion of this system is in a state of maximum distention, while its more distal segments still retain their diastolic caliber. A moment thereafter, however, these conditions are reversed, the advancing wave causing the peripheral portion to become distended, while the more central portions recoil and bring their elastic power to bear upon the blood within them. The pulse, therefore, is essentially a reproduction of the changes in pressure, modified by the elastic qualities of the arterial wall.

Each systole of the heart generates a certain amount of energy which is transferred in part to the arterial wall where it is stored as potential energy, to be made use of subsequently during the diastolic period of the organ. As the cardiac energy is transmitted at regular intervals, this elastic recoil of the arteries must also occur at regular intervals. It is betrayed externally by an alternate expansion and shrinkage of the arteries, or "pulse," which is most manifest near

the heart and gradually becomes less apparent in the direction of the distal channels. In the capillaries, these pulse waves are usually not in evidence, because the friction encountered in this particular division of the vascular system is so great that the fluctuations in pressure are completely neutralized. But, in the event of a capillary dilatation, this resistance is usually diminished to such an extent that the individual pulsations are able to extend directly into the distalmost veins. This phenomenon is often observed in glands during secretion, because their activity necessitates a copious supply of blood and hence, an injected state of their capillaries. In the submaxillary gland, this vasodilatation may be produced by stimulation of the chorda tympani nerve. The arterial pulse is then clearly visible in the small vein draining this organ.

FIG. 198.—SPHYGMOGRAM FROM THE RADIAL ARTERY, DUDGEON SPHYGMOGRAPH.
D, the dicrotic wave; *P*, the predicrotic wave. (Howell.)

The Frequency of the Arterial Pulse.—It is evident that the number of the pulse-waves must coincide precisely with the frequency of the heart, because the cardiac output forms the basis of these oscillations. For this reason, the palpation of the pulse in such arteries as the radial, brachial, temporal, or carotid, is practised primarily for the purpose of ascertaining the cardiac frequency. As this topic has been dealt with at length in a preceding chapter, it need not be discussed further at this time. Attention should, however, be called to one or two points of clinical value.

Under certain abnormal conditions, it may happen that some of the ventricular contractions do not develop a power sufficient to raise the semilunar valve flaps, or, if they do, are quite unable to overcome the general arterial pressure. In the first instance, the cardiac efforts fail absolutely in producing pulse-waves, and in the second, in sustaining them for any considerable distance. This is generally true of the so-called extrasystoles which, as the name indicates, are special contractions interposed between the regular ones. As long as these extra efforts of the ventricles do not interfere with the general rhythm and output of the heart, no circulatory disturbances result. In further illustration of this fact, that the frequency of the pulse does not always indicate the rate of the heart, might be mentioned the condition of heart-block, during which, as has been stated above, the auricular rate is maintained, while the number of the ventricular contractions is diminished. Thus, it may be gathered that the best policy is to bring

the arterial pulse into relation with the apex-beat, as well as with the venous pulse. The latter is generally noted in the region of the central end of the right external jugular vein and is, of course, indicative of the rate of the auricles. In this way it is possible to detect immediately any dissociation in the rhythm of the heart.

The Velocity of the Arterial Pulse.—The fact that the pulse progresses as a wave,¹ may readily be proved by the simultaneous palpation of the carotid and radial arteries, because, as the former blood-vessel lies closer to the heart, the characteristic systolic bump will be noted sooner here than in the latter region. The interval, however, is so brief that only a practised observer will be able to perceive it. A more plastic way of demonstrating the wave-like character of the pulse is furnished by the graphic method. Two receiving tambours which in turn are connected with two recording tambours, are placed upon an artery at different distances from the heart. Upon being permitted to record in the same vertical line, it will be found that the lever nearest the heart is always raised first, and naturally, the difference in time between the upstrokes of the two levers is the time which the pulse-wave requires in traversing the segment of the artery situated between them. Having determined this distance, it is a simple matter to calculate the velocity of this wave.

While it may be said that the rate of progression of the pulse is fairly constant, its speed must differ somewhat from moment to moment, because the conditions in the vascular system are subject to frequent changes. This is especially true of the elastic coefficient of the arterial wall. Thus, it may be inferred that its velocity increases whenever the arterial pressure is raised and decreases whenever the latter is diminished.² These differences may readily be demonstrated by the repeated stimulation of the vagus nerve which procedure is followed by a fall in pressure incurred by the diastolic tendency of the heart. For very similar reasons the velocity of the pulse is also decreased during sleep and anesthesia. The difference may amount to 1 m. per second and more. Concurrently, it may be reasoned that a lessening of the distensibility of the arteries must induce a greater velocity of this wave. A condition of this kind arises, for example, during arterio-sclerosis. Landois,³ Edgren,⁴ and others have found values ranging between 6.5 and 9.0 m. in a second. The arteries used for these determinations were the carotid and femoral or the carotid and radial. It has also been noted that the velocity of the pulse is somewhat greater in the blood-vessels of the arm than in those arising from the descending aorta. It seems that 7 m. per second may be regarded as a fair average value.

¹ Discovered by Erasistratus, but denied by Galenus. It remained obscure until the time of Haller. In 1850 E. H. Weber made the first attempts to determine its velocity.

² Moens, *Die Pulskurve*, Leyden, 1878.

³ *Lehre vom Arterienpuls*, Berlin, 1872.

⁴ *Skand. Archiv für Physiol.*, i, 1889, 67.

In this connection the student is cautioned against confounding the velocity of the pulse-wave with the velocity of the blood-stream. The latter is seldom greater than 0.5 m. in a second. Thus, a stone thrown into a river produces ripples upon its surface which progress in all directions with a speed which is not at all identical with that of the flow of this body of water. This must be so, because the production of a current necessitates the bodily onward movement of the different particles of water in a definite direction, while a ripple merely indicates the passage of a wave incited by changes in the position of a relatively small number of these particles. The wave, therefore, is enabled to attain a much greater speed and to progress even against the stream. While this phenomenon cannot be said to be identical with the arterial pulse, the stone thrown into the river, really plays a part similar to that of the ventricular discharge, in consequence of which those differences in pressure are established which give rise to the elastic excursions of the arterial wall. A much better way of proving this point is to take a fairly long piece of band-tubing which is connected at regular distances with a number of vertical glass tubes. If this tubing is now filled with water by the rhythmic compression of a rubber bulb, every addition of water gives rise to a wave which may easily be traced through this system, because it induces a successive oscillation of the fluid in the different collaterals.

It is possible to ascertain the length of the pulse-wave by multiplying the velocity of transmission with the time required by the wave to pass a certain point. The former value is 7 m. per second and the latter 0.8 sec., because each pulse-wave occupies the time of a cardiac cycle, *i.e.*, it begins with the systolic discharge and ends immediately before the succeeding one. The value so found is 5.6 m. It may therefore be concluded that each pulse wave arrives at the periphery of the arterial system long before its completion at its point of origin in the aorta.

The Registration of the Arterial Pulse. Sphygmography.—It has previously been shown that the cardiac variations in arterial pressure may be registered without difficulty by connecting the artery with a mercury manometer. It is true, however, that the minute details of these oscillations cannot be depicted in this manner, because the mercury is altogether too sluggish to follow the variations in pressure with accuracy. It is best, therefore, to employ a membrane manometer or an optical manometer, such as have been described by Hürthle and O. Frank. When properly dampened, these instruments combine a slight inertia with an exceptionally high speed of reaction.

The graphic method of investigating the pulse was first employed by Vierordt¹ in 1885, but the instrument which he devised for this purpose is not well suited for this kind of work, owing to its relative inelasticity. A much more sensitive instrument has been constructed

¹Lehre vom Arterienpuls, Braunschweig, 1855.

by Marey,¹ to which the name of sphygmograph has been given. Although variously modified in subsequent years, the principle involved in its construction has not been changed.

A pelotte, attached to a steel spring, is placed upon the skin over the radial artery in such a way that the pulsations of this blood-vessel are communicated

FIG. 199.—SCHEMA ILLUSTRATING THE SPHYGMOGRAPH OF MAREY.

B, pelotte applied to blood-vessel; *W*, toothed wheel fitting into toothed rod; *R*, the up and down movements of this rod give rise to a back and forth movement of the wheel; to its axis is attached a writing lever (*L*) registering its excursions upon a kymograph (*K*).

to it directly. But as the excursions executed by the arterial wall and overlying tissues are relatively small, it is necessary to magnify the movements of the sphygmograph considerably by increasing the leverage of its writing lever. The latter must be very light and a certain resistance must be imparted to it, otherwise

FIG. 200.

FIG. 200.—THE DUDGEON SPHYGMOGRAPH IN POSITION.

FIG. 201.

FIG. 201.—DIAGRAM ILLUSTRATING THE ACTION OF DUDGEON'S SPHYGMOGRAPH. (Howell.)

The lever of the Dudgeon sphygmograph: *P*, the button of the spring *F*, to be placed upon the artery. The movement is transmitted to the lever, *F*₁, and thence to the bent lever, *F*₂, the movement of which is effected through the weight, *g*. The writing point *S*, of this lever makes the record on the smoked surface, *A*.

its movements may be much exaggerated by inertia. In the instrument of Czermak,² the place of the recording lever is taken by a mirror by means of which a beam of light is reflected upon sensitive paper moved at an appropriate speed.

¹ Jour. de la physiol., iii, 1860.

² Sitzungsab. der Akad. der Wissensch., Wien, 1863.

Dudgeon and Jaquet¹ have modified this instrument by adding a time marker and an arrangement by means of which a narrow plate of blackened glass is moved past the recording needle. But as the length of this recording surface must necessarily be limited, it does not permit of the taking of long-continued records. This disadvantage is not present in those instruments which consist of a receiving and a recording tambour, the former being equipped with a button-like projection which is placed directly over the artery.² As the recording drum of this instrument may be adjusted to a kymograph at some distance from the artery, it is possible to obtain long and uninterrupted records. The so-called angiometer of Hürthle has been devised to register the pulsations of blood-vessels when fully exposed to the view. The vessel itself is held in a metal groove, while a pellote is placed upon its upper border. The latter is connected with a writing lever by means of a slender rod.

Character of the Arterial Pulse Wave. Sphygmogram.—The curve recorded by a sphygmograph is designated as a sphygmogram. It

FIG. 202.—THE CHARACTER OF THE ARTERIAL PULSE.

AB, anacrotic limb; BC, catacrotic limb; B, apex; D, dicrotic wave; N, dicrotic notch; E, predicrotic wave; F, postdicrotic waves.

gives information regarding (a) the frequency, (b) the rhythm, (c) the amplitude, and (d) the dicrotism of the pulse. Each pulsation begins with an ascent which is the counterpart of the rise in systolic pressure. Furthermore, as the ventricle discharges its contents rather quickly, this upstroke must necessarily be steep. The curve attains its greatest height at the point of greatest distention of the artery, forming here the so-called apex. It then declines slowly until the following systole of the heart again sends it abruptly upward. In contradistinction to the almost vertical upstroke, the downstroke slants considerably, because, being opposed by a high capillary resistance, the recoil of the distended arteries cannot give rise to a perfectly free escape of blood into the capillaries and veins. Each wave of the pulse, therefore, consists essentially of two phases, its ascending portion being designated as the anacrotic limb, and its descending portion as the catacrotic limb.

Keeping these facts clearly in mind, we are now in a position to consider some of its minor details (Fig. 202). The *anacrotic limb*

¹ Zeitschr. für Biologie, xxviii, 1891. A description of the sphygmograph of Petter and Frank is given in this Journal, xlix, 1907, 70.

² Brondgeest, Onderz. gedaan in het physiol. Lab. d. Utrecht. Derde Reeks, ii, 1873.

(*A-B*) is generally smooth; its steepness, however, varies with the tension prevailing in the arteries. If the pressure is high, the ascent must be slower, because it is then developed against a greater resistance. A low pressure, on the other hand, favors a more rapid rise in pressure and hence, also the production of a more vertical anacrotic limb. It should also be remembered that if the resistance in the arterial system is high, the upstroke frequently shows certain secondary waves which indicate the occurrence of an elastic quivering. Conditions of this kind are encountered in arteriosclerosis and stenosis of the semi-lunar valves. These extra oscillations which are generally situated near the apex of the curve, are known as anacrotic waves. In accordance with the preceding statement, it may be assumed that they are tension-waves, *i.e.*, quick reflections from the periphery. This view was first expressed by v. Kries,¹ who produced them in the radial artery by raising the hand to such a level that the static effects permitted the occurrence of reflections from the periphery before the summit of the pulse-curve had been reached. Obviously, any condition which hinders the quick emptying of the ventricles, must give sufficient time for these reflections to develop. They are especially prone to occur in aortic stenosis when the narrowing of the aortic orifice is associated with a hypertrophy of the ventricular musculature.

The *apex* (*B*) of the normal pulse-wave possesses a rounded outline, while in the sphygmogram it is generally very pointed. This discrepancy must be attributed to an instrumental error, namely, to the "fling" which is imparted to the lever and its connecting parts whenever the artery is suddenly expanded. When especially conspicuous it is called the "percussion-wave."

The *catacrotic limb* (*B-C*) exhibits several details which deserve a more lengthy discussion. Its most constant characteristic is a well-marked secondary rise which appears near the middle of the descent and is known as the *dicrotic wave* (*D*). Subsequent to this point a number of smaller wavelets are usually observed which are designated as the *postdicrotic waves* (*F*). Immediately preceding the dicrotic wave, a small oscillation is generally obtained which is called the *predicrotic wave* (*E*). Between points *E* and *F*, the curve shows a depression, known as the *dicrotic notch* (*n*).

While the dicrotic character of the pulse was recognized by palpation long before the invention of the sphygmograph, its dicrotism was first demonstrated in a plastic manner by Thelius in 1850.² Some-time later Marey³ obtained graphic records of it, while Landois⁴ proved its existence by pricking an artery with a needle and by permitting the blood to spurt against the paper of a slowly revolving kymograph. Records of this kind are called *hematograms*.

¹ Studien zur Pulslehre, 1892.

² Vierteljahrschr. für prakt. Heilkunde, xxi, 1850.

³ Jour. de la Physiol., iii, 1860.

⁴ Pfüger's Archiv, ix, 1874.

A pronounced dicrotism of the pulse usually indicates a low blood pressure, because a low tension permits the systolic-diastolic differences and other fluctuations in pressure to become extreme. Conditions of this kind frequently develop in the course of many wasting diseases, and especially during fevers, such as typhoid, when a low peripheral resistance is associated with an, as yet, efficient pumping force of the heart. Any factor, therefore, which induces sudden and extreme variations in pressure, or favors the elastic resiliency of the arterial wall must tend to augment the dicrotism. For this reason, it is usually very conspicuous in young people, but not in adults and older persons, because their arteries have been rendered more rigid by calcareous infiltration.

Any discussion as to the cause of the dicrotic wave must first of all take into account that it may be a reflection traveling from the heart outward, or that it may be a peripheral reflection passing inward. The second possibility may be disposed of very quickly, because if it really were a centripetal wave, it should be possible to obtain it apart from the principal wave of the pulse. The latter has been proven to be of central origin. Now, since the dicrotic elevation always keeps at a definite distance from the apex of the primary wave, we are entirely justified in concluding that it originates centrally and represents, therefore, a centrifugal wave, traveling at the same velocity as the principal one.

Having established the direction of the dicrotic wavelet, it now becomes a relatively simple matter to detect its cause. As may readily be surmised, the latter must be sought in the closure of the semilunar valves. A thorough distention of the aorta having been attained, its walls recoil immediately upon the completion of the ventricular systole and place the blood within under continued pressure. The blood then seeks to escape in the direction of least resistance, namely, toward the capillaries as well as toward the heart. The centripetal movement of the column of blood is at first greatly facilitated by the negativity resulting in the root of the aorta in consequence of the ventricular discharge, but is suddenly cut short by the approximation of the aortic semilunar valve-flaps. Being thus suddenly thrown against the closed semilunar valve, a reflection results which is conveyed toward the periphery in the form of a wavelet superimposed upon the principal wave.

The dicrotic notch immediately preceding the dicrotic elevation, seems to have its origin in the decrease in pressure resulting in the root of the aorta at the beginning of ventricular diastole. As the aortic walls recoil and force the blood against the closed semilunar valves, a slight downward deviation of the latter results, because they are no longer supported by the firmly contracted ventricular musculature. This yielding of the "semilunar floor," however, is very limited and soon gives way to a rebound of the blood which in turn causes the distention of the aorta described a moment ago as the dicrotic wave.

The predicrotic wave or waves appear to be exaggerations of the recoil produced by the "fling" of the writing lever, but, contrary to the inertia which gives rise to the pointed apex, or percussion-wave, these secondary elevations are not dependent upon the initial upward throw of the lever, but upon its rebound as it again endeavors to assume the resting position. These oscillations, however, are destroyed very shortly by the negative variation appearing in the form of the dicrotic notch. The postdicrotic wavelets have also been regarded as inertia movements of the instrument. It is more than probable that the dicrotic elevation suffers an exaggeration in the same way as the primary wave and hence, the writing lever and its connecting parts can assume their position of rest only after they have passed through several adjusting oscillations. Another view is that they represent after-vibrations of the column of blood following in the wake of the dicrotic wave.

It should also be remembered that the tracings of the pulse taken from different arteries, show certain differences regarding these minor fluctuations. In explanation of this phenomenon it has been suggested by Frank¹ that certain regions of the vascular system are so shaped that they are capable of giving rise to special types of reflections which then tend to modify the character of the principal pulse-wave. Thus, it has been stated that the carotid pulse is influenced by waves reflected from the circle of Willis, while the pulse in the descending aorta suffers a slight modification in consequence of reflections from the bifurcation of the iliac arteries. It is true, however, that many of these secondary currents interfere with one another in such a way that they become neutralized.

Pulse Pressure.—When referring to blood pressure, we usually have its average value in mind. It has been pointed out above that this value may be determined most accurately by ascertaining the arithmetic mean of the systolic and diastolic pressures, as registered by the direct method. It may also be determined by the indirect method, but only approximately, because this estimate must be based upon the diastolic pressure. The mean pressure follows the diastolic minimum pressure more closely than the systolic maximum and hence, a greater importance is frequently attached to the former than to the latter. But as a definite numerical relationship between these factors does not exist, the average blood pressure is usually determined in a rough way by adding one-third of the systolic-diastolic difference to the diastolic pressure. It has also been estimated at 75 per cent. of the systolic pressure.

The systolic-diastolic difference in blood pressure is generally designated as the *pulse pressure*. Thus, if a systolic value of 130 mm. Hg is opposed by a diastolic value of 90 mm. Hg, the pulse pressure equals 40 mm. Hg. Keeping this fact clearly in mind, the changes which the pulse-pressure may undergo need not be considered in

¹ Tigerstedt, *Ergebn. der Physiol.*, viii, 1909.

detail, because they are identical with those exhibited by the systolic and diastolic pressures individually. It may therefore be said that it is subject to alterations in (a) the energy of the heart, (b) the peripheral resistance, (c) the elasticity of the blood-vessels, and (d) the quantity of the circulating blood.

The Clinical Significance of the Sphygmogram.—The information to be derived from a study of the sphygmogram is of slight clinical value. No doubt, if properly adjusted, the sphygmograph may serve as an accurate means for determining the frequency and rhythm of the heart, although it does not permit us to draw definite conclusions regarding the dynamical conditions prevailing in the vascular system. In the first place, the length of the individual pulse-waves, as well as their general character, may be varied considerably by technical errors committed in adjusting the instrument. Thus, it is often difficult to apply it with that degree of pressure which is required to counter-balance the systolic pressure. In the second place, it must be granted that the excursions of the instrument depend in a large measure upon the thickness of the tissues overlying the artery and upon the degree of injection of the neighboring veins. It is best, therefore, to regard the sphygmograph merely as an aid to diagnosis and to draw no rigid conclusions from its records. It is much easier, and also much safer, to base your deductions upon the methods of inspection and palpation, because by these means the frequency and regularity of the heart are made evident in a much more direct manner. In addition, these simple methods enable us to estimate the general character of the pulse-wave, and hence, also the tension prevailing in the arterial system and the efficiency of the entire circulatory mechanism. The following qualitative differences are generally ascribed to the pulse:

(a) **Frequens or Rarus.**—A pulse is characterized as quick if it surpasses the normal maximum and as slow if it falls below the normal minimum. For men, these limits lie respectively at 75 and 68 beats in a minute.

(b) **Celer or Tardus.**—Attention should first be called to the fact that these terms do not refer to the frequency of the pulse, but solely to the speed with which the individual waves are developed. Their rise and fall may be quicker or slower than normal. Pulses of the first type indicate either a relaxed condition of the vascular system, a quick escape of the arterial blood, or an undue brevity and slight force of the ventricular contraction. An especially pronounced pulse of this kind is present in aortic regurgitation, because the incompetency of this valve permits of a quick escape of arterial blood into the heart. A tardy pulse is obtained whenever the ventricular discharges encounter a high peripheral resistance.

(c) **Magnus or Parvus.**—These terms are used to describe the amplitude or volume of the different pulse-waves. A third term, namely, *pulsus inequalis*, is employed to show that the successive waves are unequal in their volume.

(d) **Durus or Mollis.**—These qualities of the pulse are independent of the condition of the arterial wall and are indicative of the tension prevailing in the arterial channels. If an undue force must be employed to compress the artery sufficiently to cause the disappearance of the pulse, it is characterized as hard. If it is readily obliterated, it is said to be soft.

(e) **Intermittens or Deficiens.**—Disturbances in the rhythm of the pulse result either in consequence of weak contractions of the heart or in consequence of

an occasional intermittency. If the former, the pulse is characterized as intermittent, and if the latter, as deficient. Clearly, the absence of the pulse in a peripheral blood-vessel does not signify that it is also absent near the heart or that the cardiac contractions have ceased altogether.

(f) **Intercurrens, Alternans, and Bigeminus.**—These types of pulses also indicate a disturbance in the cardiac rhythm. If an occasional wave is forced in between two regular ones, the pulse is said to be intercurrent. Its cause must be sought in extra systoles. A true alternating pulse consists of rhythmic waves of large and small amplitude, this abnormality being usually dependent upon a degeneration of the myocardium. The prognosis, therefore, is grave. An entirely different significance, however, must be attached to the pseudo-alternating pulse and the *pulsus bigeminus*. As these types of pulses are dependent upon extrasystoles, two waves must necessarily appear at the periphery whenever an additional contraction results, but the wave produced by the extra contraction is always smaller than the normal one. In the bigeminus variety the pulse-waves appear in couplets, *i.e.*, the normal and succeeding extra waves are separated from the neighboring ones by a definite interval. In the pseudo-alternating pulse, on the other hand, this separation is not clearly in evidence, because it is caused by extra systoles of the premature type.

B. THE CARDIAC VARIATIONS IN VENOUS BLOOD PRESSURE

The Physiological Venous Pulse.—The venous entrances to the heart are not guarded by valves; moreover, while the size of these orifices is greatly lessened during systole in consequence of the contraction of the circular layer of muscle fibers, their complete closure is not effected. For this reason it cannot surprise us to find that the auricular pressure is propagated outward into the central veins, where it influences the venous pressure as well as the flow. Thus, if a water-manometer is connected with a central vein, the level of the water immediately exhibits rhythmic fluctuations which occur synchronously with the contractions of the heart. In addition to these oscillations it also shows much larger wave-like variations which are dependent upon the respiratory movements. The finer details of these waves may be brought out more clearly by registering them with the help of a membrane manometer.

The cardiac variations in venous pressure are most manifest near the heart and gradually decrease in amplitude in the direction of the peripheral veins. They are usually absent from the abdominal portion of the inferior vena cava as well as from the distal end of the external jugular vein, but their presence in these channels depends very largely upon the force of the heart beat and the tension prevailing throughout the venous system. These changes in pressure give rise to pulsations which are generally obtained from the external jugular vein in close proximity to the aperture of the chest. Distally to this point they are usually so slight that they cannot be properly registered. Tracings of the venous pulse may also be obtained from the central veins of animals after the chest has been opened. A receiving and a recording tambour are commonly employed for this purpose. This record is known as a phlebogram.

The Speed and Character of the Physiological Venous Pulse.—In agreement with the low tension prevailing in the venous system, the physiological venous pulse does not attain a considerable velocity. Morrow¹ states that it is only 1–3 m. in a second. A study of its general outline shows that it consists of three undulations (Fig. 203). In accordance with Fredericq,² the initial elevation (*A*) is caused by the contraction of the auricle, the wave of high intra-auricular pressure being propagated into the veins. The second positive wave (*C*) is due to ventricular systole, because the auriculoventricular valves are forced upward and thus encroach upon the space of the auricles. The third rise (*V*) is dependent upon a reflection caused by the rapid influx of venous blood into the passive auricles. If this explanation is accepted, and it seems to be the most feasible one, the physiological venous pulse is to be regarded as the counterpart of the curve of intra-auricular pressure, the latter being propagated outward into the central

FIG. 203.—DIAGRAMMATIC REPRESENTATION OF THE PHYSIOL. VENOUS PULSE FROM THE CENTRAL END OF THE EXT. JUGULAR VEIN.

A, *a*-wave; *C*, *c*-wave; *V*, *v*-wave.

venous channels through the incompetent caval and pulmonary orifices. The *a*-wave is generally the largest, but if it should prove difficult at any time to differentiate these summits from one another, it is advisable to identify the *c*-wave first of all. This is a simple matter, because it merely involves the determination by auscultation or palpation of the onset of ventricular systole. For this reason, it is always safest to record the venous pulse in conjunction with the arterial pulse or the apex-beat.

In accordance with the view presented by Mackenzie,³ the changes in intra-auricular pressure should not be regarded as the sole cause of the venous pulse, because its real character is more directly determined by the pulsations occurring in the blood current of the neighboring carotid artery. If we follow the usual custom of designating the three elevations of the venous pulse as the *a*, *c* and *v* waves, it becomes evident that:

1. The *a*-wave is dependent upon the outward propagation of the principal elevation of the intra-auricular pressure and is caused, therefore, by the contraction of the auricle.

2. The *c*-wave is not identical with the second rise in the intra-auricular pressure caused by the systolic elevation of the auriculoventricular system, but is occasioned by the transfer of the pulse from the neighboring carotid artery.

¹ Pflüger's Archiv, lxxix, 1900, 442.

² Centralbl. für Physiol., xxii, 1908.

³ Study of the Pulse, London, 1912; also see: Lewis, Mechanism of the Heart Beat, London, 1911.

3. The *v*-wave appears normally from 0.1 to 0.2 second after the commencement of the *a*-wave and finds its origin in the pressure changes resulting from ventricular systole.

In view of the fact that the *c*-wave appears in the external jugular vein before the corresponding cardiac impulse has had sufficient time to make itself felt in the carotid artery, it seems that this explanation of Mackenzie cannot be correct. In this connection it should also be remembered that a venous pulse is present in the pulmonary veins, and that its cause is precisely the same as that producing these pulsations in the systemic veins.

The Pathological Venous Pulse.—This phenomenon is most commonly associated with an incompetency of the tricuspid valve, but may also appear in the pulmonary vein in consequence of mitral regurgitation. It may be surmised that this regurgitation of the blood into the auricle gives rise to a much larger *c*-wave than the normal upward

FIG. 204.—DIAGRAMMATIC REPRESENTATION OF THE PATH. VENOUS PULSE.

In tricuspid regurgitation the *C* wave is very much increased.

movement of the auriculoventricular septum could possibly produce. In fact, a severe insufficiency often increases the amplitude of this wave so greatly that it completely overlaps the *a*-wave. Under this condition, the phlebogram presents only one large initial rise which is followed by a second one, previously designated as the *v*-wave. It must be evident that the conspicuousness of

the pathological venous pulse must differ with the severity of the valvular lesion, a severe regurgitation increasing the radius of these pulsations so that they may be perceived even in the distalmost veins. The venous engorgement always accompanying the regurgitation eventually produces a hyperemic condition of different organs and preëminently of the liver. It is then possible to obtain these pulsations directly from this organ by applying a flat metal cup to the skin overlying it, but naturally, the minute details of the individual waves are difficult to record, because the intervening mass of tissue does not readily transmit the rapid oscillations in pressure. A third type of venous pulse is observed at times in the veins of glands, but only when the latter are actively secreting. These pulsations are nothing more than the arterial pulse propagated through the highly distended capillaries of the gland.

C. THE RESPIRATORY VARIATIONS IN ARTERIAL AND VENOUS BLOOD PRESSURE

The General Character of the Respiratory Variations.—Besides the small cardiac oscillations, the blood pressure also exhibits fluctuations of a much larger amplitude which occur synchronously with the

respiratory movements. It is to be noted that inspiration produces a fall in pressure in the veins and a rise in the arteries, whereas expiration causes an increase in the venous and a fall in the arterial pressure (Fig. 205). These changes are generally associated with an alteration in the cardiac rhythm, the heart beating more frequently during inspiration. Moreover, these fluctuations do not begin precisely with the onset of the respiratory movements, but somewhat later, the intervening period being about 0.2 second in duration. It happens, therefore, that the arterial rise is always continued for a brief period of time after the beginning of the expiratory motion, while the fall is prolonged right into the succeeding inspiratory phase.

The Cause of the Respiratory Variations.—After the first breath has been taken, the lungs are held in a continuous state of hyperdistention. The elastic fibers contained in them are put on the stretch and must therefore always attempt to recoil. This enables these organs to exert an elastic pull upon the chest wall as well as upon the contents of

FIG. 205.—DIAGRAMMATIC REPRESENTATION OF THE RESPIRATORY VARIATIONS IN ARTERIAL (AP) AND VENOUS PRESSURE (VP).

JE, inspiration; *EJ*, expiration. It is to be noted that the variations in pressure lag behind the onset of the respiratory movement; this interval (*JB*) being especially evident in the case of the arterial pressure.

the thoracic cavity, which is betrayed, on the one hand, by a negativity in the intrapleural pressure (-6 to -9 mm. Hg) and, on the other, by the low degrees of pressure existing in the central venous system (-5 to -15 mm. Hg). The blood-vessels situated outside the thorax are exposed to positive pressures, and hence, it cannot surprise us to find that the blood in the intrathoracic vessels is constantly exposed to this aspiratory force. But inasmuch as the arteries are relatively resistant and unyielding, they are not so severely affected as the veins.

It must be granted, therefore, that the negative pressure in the thorax favors the venous return. Moreover, as the elastic pull upon the venous trunks is greater during inspiration than during expiration, the inspiratory movement must be the more effective of the two. For this reason, it is only natural to assume that the venous pressure is decreased during inspiration and increased during expiration. It may be inferred that these changes in pressure influence the flow in

such a way that a greater quantity of blood is drawn into the central venous channels during inspiration than during expiration. Consequently, as the heart receives more blood during the former period, it is in a position to pump more blood into the arteries.¹ This explains the inspiratory rise in arterial pressure. This mechanical explanation of the respiratory variations finds support in the following conditions:

(a) It has already been stated that the heart increases its frequency during inspiration. This phenomenon may be explained in two ways. Thus, it may be assumed that it is a reflex elicited within the heart in consequence of the influx of a greater quantity of blood, or that it is due to accelerator impulses generated by the cardiac center. The latter explanation has been submitted by Fredericq, who has found that this acceleration takes place even after the mechanical influence of respiration upon the heart has been removed by opening the chest. The fact that the division of the vagi nerves destroys the acceleration immediately proves that this system is directly concerned with the production of this phenomenon. It is also interesting to note that this acceleration is more marked in persons whose nervous system is in a state of hyperirritability.

(b) The transfer of blood from the right into the left side of the heart is greatly facilitated by inspiration, because this movement permits of a greater distention of the pulmonary blood-vessels, thereby lessening the resistance in this circuit. During expiration, on the other hand, the elastic pull upon these vessels is diminished and the resistance within them increased.

(c) The inspiratory descent of the diaphragm favors the venous return from the abdominal organs, because it tends to increase the pressure in the abdominal cavity and to lessen the resistance in the thorax.²

(d) The fact that these changes may be rendered more conspicuous by increasing the amplitude of the respiratory movements is another point in favor of this explanation. Last of all, it should be taken into account that these variations are completely reversed during artificial respiration.³ This need not cause surprise, because the artificial inflation of the lungs induces conditions practically the reverse of those prevailing during normal respiration, when this organ is expanded by a force resting upon its external surface. As the air is forced into the pulmonary passage, the capillaries of the lungs are subjected to a certain pressure which tends to increase the resistance within them. This implies that the venous pressure is increased during the period of inflation, whereas the influx of blood is diminished. The deflation of the lungs, on the other hand, relieves this compression of the pulmonary capillaries and permits a more unhindered through-flow in consequence of the diminution in the resistance.

As has been emphasized by Wiggers,⁴ the respiratory variations in blood pressure may be explained without difficulty upon the basis of the circulatory changes in the lesser circuit just enumerated. Lewis,⁵ on the other hand, believes that the respiratory motions affect the heart in a direct way, and that the effect upon the arterial blood pressure varies with the type of respiration. Thus, diaphragmatic respiration is said to give an inspiratory rise and expiratory fall in arterial pressure, while a pronounced costal movement induces an inspiratory fall and expiratory rise. This result, however, is easily explained

¹ Burton-Opitz, *Am. Jour. of Physiol.*, vii, 1902, 435.

² Burton-Opitz, *ibid.*, xxxv, 1914, 64.

³ Burton-Opitz, *ibid.*, ix, 1903, 198.

⁴ *Ibid.*, xxxv, 1914.

⁵ *Ibid.*, xvi, 1906.

in another way, because Henderson¹ has shown that the exposure of the heart to a direct pressure of this kind hinders the normal filling power of this organ and hence, also the flow through the lungs. Certain discrepancies have also been found by Erlanger and Festerling,² as well as by Snyder,³ but as a more satisfactory explanation of this phenomenon has not been submitted, it seems best to adhere to the analysis previously given.

The Traube-Hering curves are rhythmic fluctuations in pressure, each of which always embraces a number of respiratory variations.⁴ They are long, but do not attain a significant height. Their con-

FIG. 206.—TRAUBE-HERING CURVES.

The time is given in seconds. The smallest pulsations represent the cardiac variations, those of intermediate size the respiratory variations, and the large waves the Traube-Hering variations.

spicuousness, however, may be increased by curarization, anemia of the bulbar centers and asphyxia. They are commonly ascribed to irradiations of impulses from the excited respiratory center to the vasomotor center.

Waves of similar character are frequently observed in normal animals and especially in those narcotized with morphin. They are known as the *Mayer curves* and find their origin in a hyperirritable condition of the vasomotor center. This hyperirritability arises in consequence of bulbar anemia, an increased venosity of the blood, irritations of the central nervous system and the administration of certain drugs, such as digitalis and strophanthus.

¹ Jour. of Physiol., xxxvii, 1908.

² Jour. of Exp. Med., xv, 1912.

³ Am. Jour. of Physiol., xxxvi, 1915.

⁴ Traube, Zentralblatt für die med. Wissensch., iii, 1865, 882.

CHAPTER XXXIII

THE BLOOD FLOW

The Volume of the Blood Stream.—If the arterial system were composed of a number of rigid tubes, each ventricular output would be forced through this system in the form of a uniform column which would come to a standstill at some distance from the heart. But as the vascular system is elastic, and is kept in a state of hyperfilling by an appropriate peripheral resistance, the different ventricular discharges must be retained temporarily near the outlet of the heart, their retention being made possible by an enlargement of the main distributing tube, the aorta. The elastic recoil immediately following this distention, then forces a portion of this blood into the more peripheral segment and from here into the adjoining one, and so on until the periphery has been reached. In this way, the conditions incited by the ventricular discharge are repeated again and again and are thus propagated throughout the arterial system. Moreover, as the blood-bed of the aorta is larger than that of its branches put together, this blood-vessel, and especially its ascending and transverse portions, serve the purpose of an elastic reservoir from which all the peripheral blood-vessels are supplied.

Soon after its emergence from the heart, the blood enters the different branches of the aortic system and is distributed to the various tissues and organs in amounts commensurate with their activity. In close proximity to the heart, the flow very nearly equals the ventricular output, only that amount of blood having been removed from it which is destined to nourish the cardiac musculature. Farther distally, however, the reduction becomes more apparent, because a considerable quantity of blood is now diverted into the blood-vessels of the head and anterior extremities. In endeavoring to obtain an idea regarding the volume of the blood stream in any particular artery, it is not sufficient to collect the blood escaping from the opened blood-vessel in a graduated cylinder, because the removal of the peripheral resistance seriously disturbs normal dynamical conditions. With a closed vascular system, two procedures are practicable which may be designated respectively as the direct and the indirect.

The direct method consists in connecting the artery with an instrument known as a current-measurer or stromuhr. The one described by Ludwig¹ is composed of two glass bulbs (*A* and *B*) which are placed upon a metal disc (*P*) and may be rotated around a common vertical axis (Fig. 207). In this way, it is possible to

¹ Stolnikow, *Archiv für Anat. und Physiol.*, 1886. This instrument has been modified by Tigerstedt, *Skand. Archiv für Physiol.*, iii, 1891.

bring the bulbs successively into communication with the cannula inserted in the central end of the artery (*C*). To begin with, one of the bulbs is filled with normal saline solution and the other with oil. The latter is first turned toward the inflow tube (*C*). On permitting the blood to flow into this instrument by removing the clip temporarily placed upon the central end of the artery, the oil is forced upward and through the connecting tube into the limb containing the saline solution. When the latter has been completely driven into the peripheral end of the artery, the bulbs are quickly reversed so that the oil is again brought into direct communication with the influx, while the blood is forced into distant arterial channels. In order to obtain the volume of the blood stream it is necessary to record the number of revolutions of the stromuhr in conjunction with the time. Thus, if the capacity of the bulb is 5 c.c. and it has been filled 12 times in the course of one minute, then 60 c.c. of blood have passed this point of the artery in the course of this period.

Much more serviceable instruments for the calibration of the blood stream have been devised by Hürthle¹ and Burton-Opitz.² Both types of instruments contain a piston which moves within a cylinder and records its excursions upon the paper of a kymograph. For this reason, they are known as recording stromuhrs. The cylinder of the instrument described by Burton-Opitz is adjusted horizontally at the level of the blood-vessel, while the resistance of the piston is minimized by counterpoising (Fig. 208). By means of a double U-shaped valve with which the central and peripheral segments of the blood-vessel are connected, the blood may be diverted either into the compartment to the left or to the right of the piston. The piston is thus forced to move successively from left to right, and from right to left, its movements being recorded upon the kymograph by means of a lever and connecting string. This instrument having been properly calibrated, the quantity of blood which has traversed it may be read off directly from the paper. Naturally, the insertion of the stromuhr necessitates a temporary interruption of the blood flow in this vessel, but unless unduly prolonged, normal conditions are generally reestablished within a few moments after the removal of the clips. As the instrument is filled with normal saline solution, and as

FIG. 207.—LUDWIG'S STROMUHR.

a, is filled with oil to the mark (c.c.), while *b* and the neck are filled with salt solution or defibrinated blood; *p*, the movable plate by means of which the bulbs may be turned through 180 degrees; *cc*, for the cannulas inserted into the artery; *s*, the thumb screw for turning the bulbs; *h*, the holder. When in place the clamps on the arteries are removed, blood flows through *c* into *a*, driving out the oil and forcing the salt solution in *b* into the head end of the artery through *c'*. When the blood entering *a* reaches the mark, the bulbs are turned through 180 degrees so that *b* lies over *c*. The blood flows into *b* and drives the oil back into *a*. When it just fills this bulb, they are again rotated through 180 degrees, and soon. (Howell.)

¹ Pfüger's Archiv, xcvii, 1903, 193.

² Ibid., cxxi, 1908, 150. Ishikawa and Starling have described a current measurer of which a siphon forms the essential part.

the blood entering it is always returned into the vascular system by way of its distal cannula, the volume of the circulating blood must remain the same. All in all, it seems fair to state that the objections which may be raised against the use of this instrument (Starling) are in no way more valid than those raised against the employment of manometers or physiological apparatus of a similar kind.¹

FIG. 208.—DIAGRAM OF RECORDING STROMUHR.

C, cylinder; *K*, piston; *F*, piston-rod; *AR* and *AR'*, tubes for influx of blood; *A*, double U-shaped valve connected with blood-vessel at *B* and *B'*; *D1* and *D2*, positions occupied by valve when blood is directed either into the left or right side of the cylinder; *Ro*, *Sf*, *H* and *St*, apparatus required for registering the excursions of the piston upon the paper of the kymograph.

An idea regarding the volume of the blood flow may be obtained from the accompanying table which embraces the results of a series of experiments made by Burton-Opitz² and Tschuowsky.³ The values here given are calculated for a dog weighing about 15 kg.:

¹ An optical stromuhr has been described by Hürthle in Pfüger's Archiv, cxlvii, 1912, 509.

² Pfüger's Archiv, cxxix, 1909, 189, and Quart. Jour. of Exp. Physiol., vii, 1913, 57.

³ Ibid., xcvi, 1903, 214.

	c.c. in a second	c.c. in a minute
Carotid artery.....	2.53	150
Femoral artery.....	0.87	52
Hepatic artery.....	2.39	143
Thyroid artery.....	0.37	22
Ext. jugular vein.....	2.40	144
Renal vein.....	1.64	98
Mesenteric vein.....	2.74	164
Splenic vein.....	0.95	57
Portal vein.....	4.56	273
Femoral vein.....	0.85	51

The *indirect method* of measuring the blood flow embraces several different procedures, namely, the calorimetric, plethysmographic, and the gas-analytical. The *calorimetric method* devised by Stewart¹ arrives at the quantity of blood traversing a part, by measuring the amount of heat liberated by it in a certain

FIG. 209.—CALORIMETRIC METHOD OF MEASURING BLOOD-FLOW IN HANDS. (From Stewart's "A Manual of Physiology," William Wood and Co., Publishers.)

period of time and by ascertaining the difference in the temperatures between the inflowing and outflowing blood. This method is applicable to the human being. Having established the basal temperature by immersing the hands or feet for some time in water, the temperature of which is one or two degrees below that of the arterial blood, they are rapidly transferred to a calorimeter filled with water of the same temperature. As the parts are kept motionless, the heat given off by them while in this compartment, must be derived chiefly from the blood passing through them. The temperature of the arterial blood at the wrist was found to be lower by 0.5° C. than that of the rectum, while the venous blood exhibited a temperature

¹ Cleveland Med. Jour., x, 1911, and Heart, iii, 1911.

only a fraction of a degree above that of the water in which the parts were immersed. The flow is calculated in grammes per minute in accordance with the formula:

$$Q = \frac{H}{M(T - T')} \frac{1}{S}$$

Q being the quantity of blood, H the number of small calories given off in M minutes, T the temperature of the entering blood, T' the temperature of the out-flowing blood, and S the specific heat of the blood. The volume of the hands or

FIG. 210.—KIDNEY ONCOMETER.

I, the kidney is placed into the oncometer consisting of two hemispherical parts, connected with a recording tambour (T). *II*, the sides of this oncometer are lined with rubber membrane, the space between the membrane and the metal wall being filled with water of 37° C. The upper bag is connected with a recording tambour.

feet is measured by permitting them to displace an equal quantity of water from a graduated receptacle. The bloodflow is expressed in grammes per 100 c.c. of tissue per minute.

These tests upon the hands of normal individuals have given the average value of 5.5 grammes of blood per 100 c.c. of hand-volume in a minute, but naturally, this figure is subject to considerable variations, because the vascularity of a part may be changed at any time either by influences brought to bear upon it directly, or,

FIG. 211.—DIAGRAM OF SCHÄFER'S AIR PLETHYSMOGRAPH (SPLENIC ONCOMETER).

P , box for insertion of spleen; R , piston-recorder; L , writing lever.

in an indirect way, by reactions occurring in other regions of the body. In a robust young man the average flow amounted to 12.8 grammes per 100 c.c. of hand per minute for the right hand and to 12.3 grammes for the left. In the foot, the flow per unit of volume of the part is smaller than in the hand. In the forearm the flow is much less than in the hand (Hewlett).

The blood supply of an organ may also be determined in an approximate way

by the *plethysmographic method*.¹ The part to be experimented upon is enclosed in a rigid capsule, known as a plethysmograph, which is then connected with a volume recorder or an ordinary tambour. The shape of this instrument, however, must necessarily be changed to suit the anatomical peculiarities of the organ. We have so far been placed in possession of plethysmographs for the kidney, spleen, heart, lung, liver, brain and the anterior and posterior extremities. Special names have been given to these; the one for the heart being designated as a cardiometer, and the one for the kidney as a kidney oncometer, in contradistinction, for example, to the splenic and hepatic oncometers.

The principle of plethysmography may be illustrated with the help of the cranial cavity. If the skull is trephined, and the trephine-opening connected with a recording drum, the variations in the volume of the brain coincident with the various bodily activities, may be accurately followed upon the paper of a kymograph.² This same procedure may be practised upon any other organ provided, of

FIG. 212.—BRODIE'S RECORDER.

A, rubber pouch; R, is placed between two plates A and B; the latter is equipped with a writing lever.

FIG. 213.—A SCHEMATIC DIAGRAM OF MOSSO'S PLETHYSMOGRAPH FOR THE ARMS

a, The glass cylinder for the arm, with rubber sleeve and two openings for filling with warm water; s, the spiral spring supporting the test tube, t. The spring is so calibrated that the level of the liquid in the test tube above the arm remains unchanged as the tube is filled or emptied. The movements of the tube are recorded on a drum by the writing point, p. (Howell.)

course, that its shape and position permit of its being enveloped by a rigid capsule. Air transmission or fluid transmission may be employed, and the organ may be

¹ For a full description, see: François-Frank, in Marey's *Travaux du Laboratoire*, 1876.

² Suggested by Hallion and Comte, *Arch. de Phys. norm. et pathol.*, 1894.

exposed to the medium directly, as in Mosso's instrument,¹ or may first be surrounded by an envelope of soft rubber (Fig. 210). The changes in volume which the organ undergoes may be recorded by means of an ordinary U-shaped manometer filled with water, or with the help of tambours of the type designed by Marey and Hürthle, and the piston-recorders constructed in accordance with the suggestions of Roy,² Ellis,³ Schäfer,⁴ Hürthle,⁵ and Lombard.⁶ A very convenient and practical recorder has been described by Brodie,⁷ the essential constituent of which is a pair of bellows made of thinnest rubber and equipped with a delicate writing lever. A plethysmograph, which is frequently made use of in the laboratory, is the one designed for the reception of the hand and forearm (Figs. 213 and 214). It consists of a cylindrical chamber of glass which is filled with warm water through two openings in its upper wall. The space around the arm is made air-tight by a cuff of

FIG. 214.—DETAILED DRAWING OF THE GLASS PLETHYSMOGRAPH WITH RUBBER GLOVE TO PREVENT ESCAPE OF WATER.

2, The glove with its gauntlet reflected over the end of the glass cylinder; 1 and 3, supporting pieces of stout rubber tubing; *D* and *E*, sections of outer and inner rings of hard rubber to fasten the reflected rubber tubing and reduce the opening for the arm. (*Howell*.)

rubber membrane which is adjusted in such a way that it does not compress the blood-vessels of this locality. The small orifice in the far end of this cylinder is connected with the recording instrument. This arrangement allows any change in the volume of the arm to cause a corresponding displacement of the water which in turn varies the level of the recording lever.

The uses to which this instrument may be put are very manifold. It has been stated above that the cardiometer may be employed to determine the volume of the output of the heart by obtaining the differences in the volume-curve of this organ during systole and diastole. In a similar way the attempt has been made by Brodie to measure the blood supply of the kidney by temporarily blocking its venous return and recording the increase in volume occurring at this time. The

¹ *Diagnostik des Pulses*, Leipzig, 1879.

² *Jour. of Physiol.*, iii, 1880, 203.

³ *Ibid.*, vii, 1886, 309.

⁴ *Ibid.*, xx, 1896, 1.

⁵ *Pflüger's Archiv*, liii, 1893.

⁶ *Am. Jour. of Physiol.*, iii, 1890.

⁷ *Jour. of Physiol.*, xxvii, 1902. A very simple method of registration has been described by O. Müller (*Archiv für Anat. und Physiol.*, 1904, Suppl.).

supposition in determinations of this kind is that the venous drainage balances the arterial influx and that an increase or decrease in the volume of an organ may be taken as a measure of its vascularity. This inference may be a safe one to make when dealing with passive and compact organs, but may lead to errors if the part experimented upon is soft in texture and embraces varying amounts of active tissue elements. The plethysmograph has also been employed for the registration of those changes in the volume of parts which occur in consequence of the activity of the heart or respiration, and also in consequence of different experimental procedures. In all these cases it is assumed that the alterations in the volume of a part are dependent upon displacements of fluid and are therefore directly attributable to changes in its blood supply. When a study is made of the volume-curve of the arm it will be seen to be made up of smaller and larger oscillations, the first of which occur synchronously with the action of the heart, and the second, with the respiratory motions. This means that the systolic discharge of the heart increases the vascularity of this part momentarily and that a similar increase takes place throughout inspiration. A most striking demonstration of these

FIG. 215.—PLETHYSMOGRAPHIC CURVE OF FOREARM.

Showing the cardiac and respiratory variations in the volume of the arm. The decided decrease in its volume observed here is due to mental activity; hence, to a transfer of blood from the cutaneous circuits into that of the cerebrum. (Howell.)

changes may be had by observing the surface of the brain through a rather small trephine opening which contains a small quantity of warmed saline solution. The level of the solution will be seen to rise with every systole and to fluctuate in larger waves with every respiration.

When taken with a fairly sensitive apparatus, the general appearance of the volume-curve of a part presents practically the same details as a tracing of the blood pressure. It displays not only the cardiac and respiratory oscillations, but also Traube-Hering waves and all those variations which are dependent upon more lasting increases or decreases in the blood supply. In this way, for example, it has been demonstrated by Mosso that the vascularity of the brain is diminished during sleep, because the intracranial blood is transferred during this period into other circuits of the body.

The *chemical method* which has been introduced by Bornstein¹ is founded upon the principle that the volume of blood passing through the lungs of a man may be obtained by calculation from the quantity of nitrogen absorbed by the blood. This value is derived from the tension difference of this gas in the alveolar air and the blood. Zuntz and his co-workers,² as well as Krogh and Lindhard,³ employed

¹ Pfüger's Archiv, xxxii, 1900.

² Zeitschr. für Balneologie, iv, 1912.

³ Skand. Archiv für Physiol., xxvii, 1912, 100.

nitrous oxid instead of nitrogen. A similar procedure has been followed by Boothby¹ who has determined the minute-volume of the pulmonary blood stream of man during rest and muscular exercise. These experiments have shown that the total blood flow through the lungs amounts to more than 3 liters in a minute, and hence, about 60 c.c. of blood must be discharged by each systole of the heart. But this figure may be varied somewhat by changes in posture, muscular work, and a more thorough ventilation of the lungs and consumption of oxygen.

The Velocity of the Blood Flow.—We have seen that the main purpose of the circulation is to supply the different colonies of cells with nutritive material and to remove from them all those substances which are of no further use to them. This interchange occurs in the capillaries, where the blood and the body-fluid are separated from one another by only a very thin layer of cells. These tubules, therefore, are of much greater metabolic value than the arteries and veins. The latter merely play the part of supply channels.

The systemic and pulmonary circuits arise from single tubes, the repeated division and subdivision of which eventually gives rise to an intricate network of the finest possible tubules, the capillaries (Fig. 216). The gradual reunion of these in turn leads to the formation of large collecting channels which are finally united in a common reservoir, the auricles. It should be remembered, however, that the total cross-section of the vascular system increases constantly in the direction of the capillaries, but diminishes again distally to these, and the more so the closer we approach the heart. The smallest blood-beds, therefore, are found at the aorta and at the venæ

FIG. 216.—DIAGRAM TO ILLUSTRATE THE CHANGES IN THE CROSS-SECTION OF THE VASCULAR SYSTEM.

A, aorta; Ar, arteries; C, capillaries; V, veins; VC, venæ cava.

cavæ. The latter, however, is somewhat larger than the former. Their peripheral ramifications put together represent a blood-bed which is very much larger than that of either the arteries or veins. As has just been stated, the blood-bed again decreases in size on the other side of the capillaries, because while the sectional areas of the different single veins increase constantly as they unite into larger channels, their combined area becomes less. Consequently, the size of the vascular system at the venæ cavæ is almost as small as that at the aorta. It is also of interest to note that the blood-bed of the aorta is somewhat larger than that of all the arteries combined, which fact again tends to show that the aorta serves as the elastic reservoir of the circulatory system.

As far as the velocity of the blood flow is concerned, the preceding statements must show immediately that the speed of flow is greatest

¹ Am. Jour. of Physiol., xxxvii, 1915, 383.

in the arteries, least in the capillaries, and intermediate in the veins. (Fig. 217). These changes in the flow, as we shall see later, are in no way different from those displayed by water while traversing a tube of varying diameter. Provided, therefore, that the quantity of the circulating blood remains the same, its speed of flow must be inversely proportional to the size of the blood-bed. It has been stated that the cross-area of the capillaries is from 600 to 800 times larger than that of the aorta. Thus, Tigerstedt estimates the capillary expanse of man at 800 to 2200 sq. cm., while Nikolai, upon the basis of a ventricular output of 75 c.c., gives the value of 1500 sq. cm. It need not surprise us, therefore, to find that a most profound reduction in the speed of the blood flow results as soon as the capillaries have been reached.

In the second place, the velocity of the flow in any tube is dependent upon the friction to which the constituents of the fluid are exposed.

FIG. 217.—DIAGRAM TO ILLUSTRATE THE RELATIONSHIP BETWEEN THE SIZE OF THE BLOOD-BED AND THE VELOCITY OF THE FLOW.

B, cross-section; *S*, speed of flow in (*A*) arteries; *C*, capillaries and (*V*) veins; *Z*, zero line.

Thus, we recognize two types of friction, namely the one produced by the fluid in coming in contact with the wall of the tube and the one produced by its molecular constituents when thrown against one another. The former is called "external" friction and the latter "internal" friction or viscosity. For this reason, the blood does not speed onward as a uniform column, but is separated into layers, the outermost of which remains stationary, while the central one, forming the core of the stream, moves ahead with the greatest possible speed. The red corpuscles and heavier elements are thus forced into the central stream, while the lateral zone is filled chiefly with plasma. Hence, in attempting to determine the speed of the blood flow under the microscope, we really measure the rate of progression of the cellular elements in the axial stream. If these could be removed, the speed of the plasma-blood would thereby be much augmented. Obviously, therefore, the solids tend to retard the flow, because they heighten the internal and external frictions.

If these two factors are now united under the general term of peripheral resistance, the further conclusion may be drawn that, every-

thing else remaining equal, the speed of flow must be least in that division of the circulatory system in which the greatest resistance is encountered. It has previously been shown that the friction is greatest in the capillaries, and hence, it may be gathered that these tubules place the greatest resistance in the path of the circulating blood. A few figures may suffice to illustrate this point. Some of the capillaries are so small that the red cells cannot enter them at all, while those which possess a diameter of $5-7\mu$, permit their passage only after they have been compressed into a shape approaching the elliptical. The larger capillaries, measuring 14μ and over in diameter, allow several erythrocytes to pass side by side. The average length of these tubules has been estimated by Tigerstedt at 0.02 cm. Moreover, if the average cross-section of a capillary is $7.5\mu^2$, a capillary area of 1500 sq. cm. would embrace two billion capillaries, placed side by side. Ordinarily, of course, the capillaries recur at distances of less than 0.02 cm.

In the arterial channels, on the other hand, the blood encounters only a relatively slight resistance, so that it is able to retain practically the entire pressure developed by the heart until it arrives in the arterioles. The blood rushes through these vessels with a considerable speed, but its function is in no way curtailed thereby, because a direct interchange between it and the neighboring cells does not take place until the capillaries proper have been reached. Here radically different conditions are met with. Since the walls of these tubules consist of a single layer of elongated and flattened cells which are only slightly thickened in the regions of the nuclei, the tissues are brought into almost immediate relationship with the blood. The latter, moreover, moves past these cells with the slowest possible speed. This is important, because it is essential that a sufficient time be allowed for the interchange of material between the blood and the lymph bathing the tissue-cells. In the veins, practically the same conditions prevail as in the arteries. The nutritive interchanges having been completed in the capillaries, the blood again rushes onward at a much greater speed, without, however, at all equaling that of the arterial stream.

The Determination of the Velocity of the Blood flow.—As the dynamical conditions in the different segments of the vascular system differ considerably, it is quite impossible to employ the same method in all cases. Volkmann (1850) has succeeded in obtaining approximate values for the speed of the arterial flow in the following way: A U-shaped glass tube of definite length and caliber is connected with the artery in such a way that the blood may be made to pass either through it or through a much shorter tube situated in the base of this instrument (Fig. 218). To begin with, the tubes of this instrument which is known as a *hemodromometer*, are filled with normal saline solution which is then forced into the circulation by the entering blood. The length of the U-tube being known, the speed of flow may be determined with-

out difficulty by simply noting the time when the blood enters and leaves its orifices.

Instruments embodying the principle of *Pitot's tubes* have been designed by Cybulski.¹ Two tubes (d and d') which have been bent at right angles, are inserted in the blood-vessel in such a way that the orifice of one points in the direction of the blood stream and that of the other against it (Fig. 219). The level of the saline solution with which they have previously been filled will then rise in the latter and

FIG. 218.

FIG. 218.—VOLKMANN'S HEMODROMOMETER.

A and B, cannulas for connecting the central and distal ends of the blood-vessel with this instrument. C, short cut through base of instrument; D, U-shaped tube of definite length. The blood may be diverted into the latter at any moment by turning the valves E and F.

FIG. 219.—DIAGRAM TO SHOW THE PRINCIPLE OF THE CYBULSKI PHOTO-HEMOTACHOMETER.

FIG. 219.

fall in the former. The push (d) and the pull (d') which the moving blood exerts upon them must, of course, be directly proportional to the speed of the flow. It need scarcely be mentioned that these variations in the levels of the liquid (h and h') may be recorded either by means of ordinary tambours connected with the ends of these tubes, or by means of a beam of reflected light.

The *hemotachometer*, devised by Chauveau and Lortet,² is another instrument of this type. It consists of a T-tube made of metal, in which a very delicate pendulum is suspended (Fig. 220). The short arm of the latter projects into the blood stream, while its long arm

¹ Pflüger's Archiv, xxxvii, 1885, 382.

² Jour. de la Physiol., iii, 1860, 695.

rests upon a millimeter scale. As the blood strikes its lower end, it is deflected in the direction of the current, its degree of deflection being clearly marked upon the scale. Naturally, this apparatus is first graduated with currents of water of known velocity. It can also be made to register its deflection by simply attaching the long arm of the pendulum to the membrane of a tambour.

The speed of the flow in the arteries and veins may also be determined with the help of the stromuhr which, as has been stated above,

FIG. 220.—THE HEMODROMOGRAPH OF CHAUCHEAU AND LORTET.

B, blood-vessel. The end of the pendulum (*P*) is played against by the blood, its deflection being registered by the receiving drum (*T*) which, in turn is connected with a recording tambour (*K*). The pendulum is contained in a cannula (*M*).

measures the quantity of blood traversing a blood-vessel in a given period of time. This calculation, however, also necessitates the determination of the internal diameter of this vessel. Burton-Opitz¹ and Tschuowsky² have made use of the following simple procedure in obtaining this value. Having ascertained the external diameter by means of calipers, the blood-vessel was gently compressed between two thin platelets of glass until it became empty. The thickness of the platelets and vessel wall was then subtracted from the external diameter, and in addition also the thickness of the platelets. The fact that the speed in the arteries is astonishingly great has been brought out by the experiments of Volkmann, Dogiel and Chauveau. The maximal speed in the carotid artery of the dog is given as 500 mm. in a second during systole and as 250 mm. during diastole. In the horse, the speed varies between 520 mm. and 150 mm. in a second, and naturally, these systolic-diastolic differences are most evident in the arteries in the immediate vicinity of the heart. In the smaller arteries the flow is quite constant. The same holds true of the capillary flow although it may be rendered remittent at any time by producing a slight obstruction centrally to the capillary area. Burton-Opitz and Tschuowsky have furnished the following average values:

Carotid artery.....	241.0 mm. in a second
Femoral artery.....	234.4 mm. in a second
Hepatic artery.....	350.0 mm. in a second

In general, therefore, it may be said that the velocity of the blood flow in the peripheral arteries amounts to 250–300 mm. in a second. It decreases somewhat in the smaller arteries, reaching its minimum

¹ Am. Jour. of Physiol., vii, 1902, 435.

² Pflüger's Archiv, xcvi, 1903, 286.

value at the arteriocapillary junction. On the venous side, such high values are not encountered under ordinary conditions. Thus, if the accompanying determinations of Burton-Opitz¹ are used as a guide, it must be concluded that the speed of the venous blood is only about one-fourth as great as that of the arterial, viz.:

Ext. jugular vein.....	80.0 mm. in a second
Renal vein.....	63.0 mm. in a second
Mesenteric vein.....	83.6 mm. in a second
Femoral vein.....	61.6 mm. in a second

It is slowest in the vicinity of the capillaries and fastest in the central veins; moreover, when the blood reaches the neighborhood of the heart, it is brought under the influence of the right auricle and shows alterations in flow similar to those encountered in the central arterial trunks. Thus, it has been proved by Burton-Opitz² that the influx into the right auricle is not constant, but is diminished during the periods of high intra-auricular pressure, *i.e.*, during the systole of the auricles and again during the systole of the ventricles. It may be surmised that the heart influences the current in the pulmonary veins in a very similar manner.

The capillaries, of course, are not accessible to any one of the instruments described previously. In the frog, however, fairly accurate results may be obtained by placing a translucent capillary area, such as the web or mesentery, under the microscope in such a way that a rather straight capillary comes to lie directly across the divisions of an ocular micrometer. The time is then determined when a certain erythrocyte enters and leaves this capillary. The length of this tubule is ascertained later on by determining the magnification, which requires a comparison of the ocular micrometer with the stage micrometer. By this procedure Weber³ and Volkmann⁴ have found the velocity of the capillary blood stream to be 0.5 to 0.8 mm. in a second.

Vierordt⁵ has also described a method which is applicable to man and depends upon the following entoptic observation. As the red cells traverse the retinal blood-vessels they cast their shadows upon the underlying rods and cones. The visual sensations set up by the latter may be rendered clearly perceptible in an indirect manner by fixedly gazing at a white surface placed at a distance of 11–16 cm. in front of the eyes. Having first determined the speed of the projected shadows upon the screen, the speed of the red cells in the retinal vessels may be ascertained in accordance with the proportion:

$$a : b = c : x; x = \frac{bc}{a}$$

¹ Pfüger's Archiv, cxxiv, 1908, 469.

² Am. Jour. of Physiol., vii, 1902, 435.

³ Archiv für Anat. und Physiol., 1838, 450.

⁴ Häemodynamik, 1850.

⁵ Archiv für physiol. Heilkunde, xv, 1856.

in which a stands for the distance between the screen and the anterior nodal point, b for the distance between the retina and the posterior nodal point, and c for the distance traversed by the projected image. Values between 0.6 and 0.9 mm. in a second have been found by this method. If it is now remembered that the length of the true capillaries varies between 0.4 and 0.7 mm., the general conclusion may be drawn that a red cell traverses a capillary of average length in about 1 second.

The Circulation Observed under the Microscope.—The study of the blood flow was made possible at an early date by the discovery of the microscope. To begin with, cold-blooded animals were employed, partly because their tissues are more accessible and resistant, and partly because their erythrocytes are much larger than those found in warm-blooded animals. These observations may be arranged in the following chronological order:

- Malpighi (1686): Lung, mesentery, urinary bladder of the frog.
- Leeuwenhoek (1689): Tail of the tadpole and fish, wing of the bat.
- Cowper (1704): Mesentery of the rabbit.
- Spallanzani (1773): Embryo of the chick.
- Hueter (1879): Mucous membrane of man.
- Ewald (1896): Lung of the triton.

When a capillary area is subjected to a magnification of about 15 diameters, it will be seen that many of its tubules are extremely small and do not permit the passage of anything more than the plasma and occasional white cells. Others, again, possess a somewhat larger caliber and allow two or three red cells placed side by side to traverse them. The most interesting picture, however, is presented in those tubules which are just sufficiently large to permit the entrance of single erythrocytes, so that it becomes possible to follow them as they wend their way in single file through these circuitous passages. In fact, in many cases these elements must be considerably elongated before they can enter these tubules. They may be thrown across a bifurcation and be rocked back and forth for some moments before they manage to escape into one or the other of these branches. The latter phenomenon, in particular, permits us to obtain a clear idea regarding the elastic properties of these elements, as well as regarding the friction and resistance which they must overcome in their journey through these tubules.

In general, it may be said that the principal characteristics of the capillary flow are its slowness and constancy. The arterial capillaries and arterioles are much larger than the capillaries proper and are, therefore, able to accommodate a much greater number of red cells. Furthermore, as the speed of flow within them is much greater, it is difficult to distinguish the individual cells. The venous capillaries and venules show essentially the same characteristics, but as the flow within them is not so rapid, the different red cells may be more easily differentiated from one another. On the arterial side, the stream

presents a clear outer zone, measuring about 0.01 mm. in width and containing only plasma and a few leukocytes, as well as a dark central zone in which the red cells are massed. The platelets occupy the peripheral layers of the stream. This arrangement is also evident in the venules, but as the venous current is less rapid, the red cells are more widely scattered and the marginal zone is not so clearly defined. In the capillaries, very naturally, the distribution of the corpuscular elements cannot be dominated so much by ordinary physical conditions, because these channels are so small that one or two erythrocytes placed side by side fill them completely. Another means of differentiating between the true capillaries and their supply and collecting tubules is presented by the color of the blood. It is darkest in the venules owing to the presence of greater amounts of carbon dioxid, and lightest in the capillaries, because the red cells are here spread out in thin layers and single cells, as has been mentioned above, are practically colorless. Still another means of differentiation is furnished by the structural appearance of the different blood-vessels. As the wall of a true capillary is composed of only a single row of flattened cells, it cannot be made out very clearly. Neither is it possible to focus a venule very sharply. The arterial capillaries, on the other hand, are generally well defined. This is especially true of the arterioles, owing to the deposition of smooth muscle cells within their wall. Moreover, these tubules generally pursue a serpentine course, whereas the venous tubules are rather straight.

The Circulation Time.—A droplet of blood leaving the left ventricle may pursue many different courses. It may enter the coronary circuit and return to its starting point within a very short time, or it may pass through the portal organs, the posterior extremity, the brain and other parts, in which cases a very much longer period of time will be required before it can again reach the cardiac vestibule. E. Hering¹ attempted to determine the time required to complete the circuit of the vascular system by introducing a chemical substance into the blood which could be easily recognized. He made use of solutions of potassium ferrocyanid which were injected into the right external jugular vein and were tested for in the blood withdrawn from the corresponding vein on the opposite side. These samples were arranged in series in accordance with the time of their withdrawal and were permitted to clot, after which the serum was tested with ferric chlorid. The results showed that the solution completed the circuit through the heart and carotid arteries in from 20 to 30 seconds. Vierordt² made use of a more accurate method for determining the length of the intervening period by permitting a series of receiving cups to rotate at a uniform speed below the vein. Hermann employed sodium ferrocyanid and permitted the blood to drop at regular intervals upon paper moistened with ferric chlorid.

¹ Zeitschr. für Physiol., iii, 1829.

² Erschein. und Gesetze der Stromgeschw. des Blutes, Frankfurt, 1858.

The circulation time for this particular circuit is: 6.6 seconds in the cat, 7.4 seconds in the rabbit, 16.3 seconds in the dog, and 28.8 seconds in the horse. For man the time for the completion of a circuit of medium length has been calculated at 23 seconds so that from 26 to 28 beats of the heart are required to effect this journey. In other words, a droplet of blood traverses the circulatory system about three times in every minute.

More recently, Stewart¹ has devised a method which is based upon changes in the electrical conductivity of the blood. The carotid artery is connected with non-polarizable electrodes, the segment between them being inserted as a resistance in one arm of a Wheatstone's bridge. As soon as a balance has been established so that the galvanometer remains at rest, a solution of sodium chlorid is injected into the external jugular vein of the opposite side. This salt serves the purpose of lessening the resistance of the blood to the electrical current. As soon as this quality of blood arrives at the point designated, the balance in the Wheatstone's bridge is lost and the galvanometric needle is deflected. The time elapsing between the injection and the moment of the deflection is determined by means of a stop-watch or an ordinary chronographic appliance. Stewart² has also employed solutions of methylene-blue which were injected into the external jugular vein and were rendered visible in the opposite carotid artery by means of transillumination upon a white sheet of paper. With the help of the first method, Stewart has also determined the time consumed by the blood in its passage through various organs. In the case of the spleen the average time is given as 10.95 seconds, and in the cases of the kidneys and lungs as 13.3 and 8.4 seconds respectively. These figures show first of all that a considerable part of the total circulation time of the blood must be apportioned to the capillary networks of these organs and secondly, that the time for the pulmonary circuit is relatively short. In man it has been estimated at 12-15 seconds. A still shorter time is required for the completion of the coronary circuit. In this connection, brief mention might also be made of the fact that the circulation time between the portal vein and the arteries amounts to about 12 seconds, and the time between the femoral or renal veins and the arteries to 16 and 13 seconds respectively.³ These figures have been obtained by measuring the interval between the injection of adrenalin and the resultant rise in arterial blood pressure.

¹ Jour. of Physiol., xv, 1894.

² Manual of Physiol., London, 1896.

³ Burton-Opitz, Am. Jour. of Physiol., xli, 1916, 91.

SECTION XI

THE NERVOUS REGULATION OF THE BLOOD-VESSELS¹

CHAPTER XXXIV

THE INNERVATION OF THE BLOOD-VESSELS OF DIFFERENT ORGANS

General Discussion.—The nervous control of the vascular system is effected by two groups of elements, one of which is concerned with the control of the activity of the heart, and the other with that of the caliber of the blood-vessels. The former, as we have seen, are acceleratory and inhibitory in their nature and are dominated by nervous elements situated in the medulla oblongata. The latter, on the other hand, are apportioned to the peripheral vascular system and regulate the size of the blood-bed. For this reason they are designated as vasomotor elements. The general arrangement of this mechanism is the same as that controlling the function of the heart. It consists of a central mass of ganglion cells and of two sets of nerve fibers which conduct either in an afferent or in an efferent

FIG. 221.—REFLEX CIRCUIT FOR VASOMOTOR ACTIONS.

¹ Vershuir (Diss. Groningen, 1766) observed that the mechanical excitation of the walls of such arteries as the carotid and femoral, led to a marked constriction of their lumen. Wedemeyer (Kreisl. des Blutes, Hanover, 1828) obtained the same results with electrical stimulation. In 1831, E. H. Weber (Archiv für Anat. und Physiol., 1847) explained the phenomenon of flushing and paling upon the basis of variations in the resistance to the blood which are brought about by the muscular contractions following nervous discharges. Claude Bernard (Compt. rend., 1851) then called attention to various vascular changes connected with the cutting of the cervical sympathetic nerve, while Brown-Séquard (Philadelphia Med. Exam., Aug., 1852) ascertained that the excitation of the proximal stump of this nerve led to a constriction of the blood-vessels. Very similar results were obtained by Waller (Compt. rend., 1853), but their publication was deferred until 1853.

R, receptors; A, afferent path; VMC, vasomotor center which is intimately connected with other centers, for example, the cardiac (CC) and respiratory centers (RC); E, efferent path; B, effector in blood-vessel. Stimulation between R and VMC gives rise to pressor and depressor effects, stimulation between VMC and B to vasoconstrictor and vasodilator effects.

direction. The former convey impulses from all parts of the body to the center and the latter, from the center to the blood-vessels (Fig. 221). But as the lumen of the blood-vessels may be either decreased or increased in size, the efferent or motor path must be composed of two types of fibers, namely, those which diminish and those which enlarge it. The former are designated as vasoconstrictors and the latter as vasodilators. In accordance with this functional division of the fibers, it is possible to look upon the vasomotor center as being composed of a vasoconstrictor and a vasodilator part.

As the afferent impulses arriving in the center are capable of producing either a vasoconstriction or a vasodilatation, the fibers conducting them are commonly designated as pressor and depressor fibers. Thus, if an impulse is generated either in the center or along the course of an efferent nerve, and produces a constriction of the blood-vessels, the reaction is spoken of as a vasoconstrictor action. Again, if the stimulation of the same constituents of the vasomotor arc leads to a dilatation of a certain area of blood-vessels, the effect is said to be vasodilator in its nature. But, if the stimulus arises in a receptor or along the course of an afferent nerve, the reaction is designated as pressor if constrictory, and as depressor, if dilatatory in its nature. The last two terms, therefore, signify that the vascular reactions have been brought about reflexly.

The Location of the Vasomotor Center.—Nerve fibers, regulating the caliber of the blood-vessels, may be contained in almost any nerve, together with fibers possessing other functions. They may also be grouped in such large numbers that they form individual nerve strings of considerable size. But whether mixed with other fibers or pursuing an independent course, they cannot be differentiated from fibers possessing a different function excepting by physiologic means. In other words, as nerve fibers bear no special points of difference in their appearance, their function must be arrived at by subjecting them to certain physiological procedures, such as mechanical and electrical stimulation.

It is a well-known fact that the division of the spinal cord in the cervical region gives rise to an extensive relaxation of the blood-vessels and a fall in the general blood pressure, while the division of the nervous system above the upper border of the medulla remains without effect. From this it may be inferred that the separation of the peripheral nerve paths from the brain occasions a loss in the tonus of the blood-vessels ordinarily imparted to them by ganglion cells situated between these two cuts. Repeated experimentation has finally led to the localization of a colony of cells in the medulla oblongata to which it has been possible to ascribe a vasoconstrictor activity.¹ In accordance with the experiments of Dittmar,² this center is bilateral and lies about the middle of the fourth ventricle in the tegmental

¹ Owsjannikow, Ber. d. sächs. Gesellsch. d. Wissensch., xxiii, 1871.

² Ber. der sächs. Akad der Wissensch., math. phys. Klasse, xxv, 1873.

region near the nucleus of the facial nerve and the superior olivary body. In the rabbit it possesses a length of 3 mm. and a breadth of 1-1.5 mm. A general vasodilator center has not been definitely located as yet, but it may be assumed to form either a part of the vasoconstrictor center or to be situated in its immediate vicinity.

Secondary centers controlling the caliber of the blood-vessels are supposed to exist at different levels of the cord, as well as in the sympathetic system, but the evidence upon which this statement is based is not very conclusive. Thus, it has been found that the tonicity of the blood-vessels is retained in a measure even after they have been separated from the central nervous system and that their tonus frequently reappears very soon after the division of the cervical segment of the spinal cord.

The Activity of the Vasomotor Center.—Under normal conditions, the activity of the vasomotor center is dependent upon an influx of extraneous impulses. The sum total of these determines the tonicity and the dynamic state of the vascular system. Its function may be continued for some time after all these different afferent impulses have been shut off, but naturally, a continued absence of these stimuli always tends toward retrogression and functional uselessness. But, besides these "external" impulses which are conducted to it by way of many different centripetal nerves, the constituents of the vasomotor center are also influenced by "internal" stimuli, such as arise in consequence of changes in its blood supply or variations in the gas content of the blood.

Thus, if the carbon dioxid of the blood is increased, as can readily be done in a curarized animal by discontinuing the artificial respiration, the general blood pressure will be seen to rise gradually until it attains a height much above normal. The pressure usually remains at this level for a considerable period of time, but declines subsequently on account of the increasing diastolic tendency of the heart. This rise is occasioned by a general constriction of the blood-vessels which is dependent upon the direct excitation of the vasoconstrictor center by the carbon dioxid. Eventually, however, the contractions of the heart lose their force, because the continuous supply of blood poor in oxygen, reduces its strength so that it is no longer able to act against the high peripheral resistance occasioned by the vasoconstriction. The blood pressure then falls in proportion to the diminution in the energy of the heart and obviously, this fall must result in spite of the fact that the blood-vessels remain in the constricted condition. If the dyspneic or asphyctic condition of the blood is now lessened by again instituting artificial respiration, the heart usually regains its vigor within a short time. This change is clearly betrayed by a rise in the blood pressure above normal. Presently, however, the relaxation of the blood-vessels following upon the restitution of the vigor of the cardiac contractions permits the pressure to become normal again. Should the dyspnea and asphyxia be continued, a narcotic and para-

lytic state eventually results which is characterized by a general vascular depression and may lead to the death of the animal.

Very similar effects may be obtained by temporarily obstructing the blood supply of the brain. In all experiments of this kind, however, it is advisable to deepen the narcosis by the administration of curare, because in the non-curarized animal, the increased respiratory movements, as well as the general muscular spasms which eventually occur in the course of the asphyxia, must tend to raise the blood pressure and to interfere with the effects of the vasoconstriction. It need scarcely be emphasized that in the case of asphyxia, the constrictor agent may be either a lack of oxygen or a superfluity of carbon dioxide.

The Distribution of the Vasomotor Fibers.—The axons derived from the cells of the vasomotor center descend in the cord and terminate at different levels in the anterior horn of the gray matter. From here connections are made with the sympathetic system by way of the rami viscerales, but naturally, as these bridges exist only in the thoracic and sacral regions of the cord, the vasomotor outpourings must necessarily be restricted to these spinal segments. It has also been found that the cerebrospinal and sympathetic systems are connected with one another by way of several of the cranial nerves, and hence, it is possible that some of the vasomotor fibers leave the central nervous system by way of these channels. At all events, it must be concluded that while the control of the blood-vessels is in last analysis a function of the cerebrospinal system, it is eventually transferred to the autonomic or sympathetic system.

After the spinal neurons have entered the sympathetic system their impulses are conveyed to the more remote ganglia by secondary neurons which in turn are connected with the blood-vessels of the thoracic, abdominal and pelvic organs. The blood-vessels of the head are reached by way of the ganglia of the thorax and the cervical sympathetic which connects the latter with the superior cervical ganglion. Obviously, therefore, the fibers conducting vasomotor impulses, are typically autonomic and form such important paths as the greater and minor splanchnic nerves, the *nervi erigentes* and the cervical sympathetic. There are, however, many blood-vessels present in our body which do not lie directly within the realm of sympathetic nerves, but are innervated by cerebrospinal nerves. In this group belong the blood-vessels of the anterior and posterior extremities. This innervation is made possible by the fact that some of the fibers leave the sympathetic system and enter the cerebrospinal nerves where they intermingle with others pursuing a perfectly straight course from the spinal gray matter to the periphery. These "recurrent" fibers form the so-called gray rami viscerales.

To summarize: the vasomotor fibers passing out from the chief center, attain the first sympathetic ganglia by way of the anterior roots of the cord, and the white rami viscerales (Fig. 222). Two or

three neurons generally cover this entire distance. They form the preganglionic path. Distally to these ganglia, the fibers constituting the postganglionic path, either continue onward to different parts of the sympathetic system, or reënter the spinal roots by way of the gray rami communicantes where they intermingle with other efferent and afferent fibers composing the different spinal nerves. In this way, even the vasomotor mechanisms situated in the domain of the cerebrospinal nerves, procure a sympathetic innervation and are rendered, therefore, characteristically autonomic.

The Location of the Motor End-organ or Effector.—It has been proved histologically that the walls of the central arteries contain much connective tissue and only a relatively small number of smooth muscle cells. In the peripheral arteries, on the other hand, the latter are much more numerous and are arranged here in the form of a massive circular (tunica media) and a thin longitudinal layer (tunica externa). No muscle tissue is present in the true capillaries, these tubules being composed solely of flat, nucleated epithelial cells similar to those found in the intima of the arteries. In the veins, connective tissue predominates, while the muscular units are poorly developed and not organized. Thus, it happens that some of the veins possess no muscle cells at all, while others, and especially those of the lower extremities, are equipped with only a very thin circular layer of these cells.

As the only effector present in the vascular system is the smooth muscle cell, it must be clear that vasomotor reactions must be restricted to those channels which are actually in possession of these elements, namely the arteries and certain veins. To be sure, it has been stated by Mall¹ that the portal vein receives a vasoconstrictor supply through the greater splanchnic nerves, but these results have been shown by Burton-Opitz² to be based upon unsatisfactory experimental evidence. Thompson,³ however, has found that the stimulation of the sciatic nerve in dogs and cats produces a visible constriction of the veins of the posterior

FIG. 222.—DIAGRAM TO ILLUSTRATE THE PATH PURSUED BY THE VASOMOTOR FIBERS.

SC, spinal cord; PR, its posterior root; AR, its anterior root; SN, spinal nerve; S, sympathetic ganglion; B, blood-vessel; preganglionic path in red; VMC, vasomotor center P (red) white ramus; postganglionic path in blue; P', directly to blood-vessel; P, recurrent fiber, reëntering spinal nerve by way of gray ramus.

¹ Archiv für Physiol., 1892, 409.

² Am. Jour. of Physiol., xxxvi, 1915, 325.

³ Archiv für Physiol., 1893; also see: Bancroft, Am. Jour. of Physiol., i, 1898, 477.

extremities, but as this effect is inconstant and very localized, it may have an indirect cause. Moreover, while Henderson¹ has found that strips of veins react toward solutions of adrenalin in the same manner as segments of arteries, this evidence cannot be considered as a direct proof of the existence of vasomotor elements in the veins. On the whole, therefore, this question seems to have found a negative solution.

As far as the capillaries are concerned, it has been shown by Stricker and others² that these tubules possess a certain degree of contractility, but it appears that this reaction cannot acquire a definite dynamical value. All living substance exhibits this property and hence, it cannot be denied to the living cells of the capillaries. Stimuli brought to bear upon them must result in a rearrangement of their contents and a possible constriction of the lumen of the capillary. This reaction, however, does not seem to be of central origin, but appears to be elicited solely by local excitations. In this connection attention should also be called to the fact that the capillary blood-bed may be materially altered by variations in the tension of the surrounding tissues. Thus, the lumen of these tubules may be compressed in consequence of the contraction of the numerous smooth muscle cells which are widely scattered through the skin. The relaxation of these muscular elements, on the other hand, must tend to widen the capillary blood-bed and to grant a more copious blood-supply to the cutaneous parts. Reactions of this kind result in consequence of variations in the temperature of the surrounding air as well as in consequence of the immersion of the body in cold or warm water. The influence of these muscular elements upon the injection of the cutaneous capillaries can scarcely be overestimated. It should be emphasized, however, that we are not dealing in this case with a true vasomotor phenomenon, but solely with a direct mechanical action. At the same time it must be granted that any influence causing a contraction of the cutaneous smooth muscle tissue, would be prone to produce a vasoconstriction in addition. A reverse relationship, however, need not exist.

In view of the evidence here presented, it seems permissible to conclude that true vasomotor actions are possible only in the arterial system. Since the smooth muscle tissue is most massive in the arterioles, it may be surmised that the most powerful effects of this kind are obtained at the arteriocapillary junction. This segment of the arterial system, therefore, gives lodgment to the gate or sluice through which the blood must pass in order to reach the capillaries. Consequently, the size of this orifice must determine the volume of the arterial escape as well as the vascularity of the more distant capillary networks. Excepting, therefore, certain local influences in the shape of the cutaneous smooth muscle cells, the caliber of the latter is determined

¹ Am. Jour. of Physiol., xxiii, 1909, 345.

² Steinach and Kahn, Pflüger's Archiv, xlvii, 1903.

exclusively by the quantities of blood which are permitted to escape through this gate.

The Nature of the Reaction.—Two views are held regarding the manner in which vasomotor changes are brought about. Thus, it may be assumed that the blood-vessels are constantly kept in a state of tonicity and that vasoconstriction is had in consequence of an extra discharge of impulses by the center, while vasodilatation is the result of a loss of tonus which is immediately followed by a passive enlargement of the blood-vessels. For this reason, the former condition may be regarded as an augmentor and the latter as an inhibitor phenomenon. A condition comparable to this one exists in the heart, where accelerator and inhibitor impulses are played against one another. The second theory proposes that vasoconstriction and vasodilatation are two distinct processes resulting in consequence of the activity of two separate mechanisms.

If the first theory is accepted, the effector need not possess special structural characteristics, because vasoconstriction could then be assigned to the contraction, and vasodilatation to the extreme relaxation of the circular musculature. But, if the second view is adhered to, two distinct effectors would have to be present, namely, one for vasoconstriction and one for vasodilatation. Regarding the former, no difficulty need arise, because it could justly be ascribed to the contraction of the circular layer of muscle cells. Less manifest is the vasodilator mechanism, because the only other available element is the layer of smooth muscle cells which is arranged longitudinally to the lumen of the blood-vessel. In the absence of a structurally more definite effector, we are practically forced to assume that these cells accomplish the dilatation either alone, or through an interaction with the circular coat.

It is quite impossible at the present time to decide with certainty whether the first or the second theory is the correct one. The evidence favoring the second view, namely, that the vasoconstrictor and vasodilator reactions are effected by separate mechanisms, is as follows:

(a) Certain nerves are in existence which possess solely a dilator function. First among these is the chorda tympani, a branch of the facial nerve, which embraces dilator fibers for the submaxillary and sublingual glands, as well as the tympanic branch of the glossopharyngeal nerve which contains dilator fibers for the posterior third of the tongue, the tonsils, pharynx, and parotid gland. In this group should also be placed the cervical sympathetic nerve, by way of which the dilators gain access to the mucous membrane of the lips, gums, palate and the skin of the cheeks and nostrils.¹ Some direct evidence is also at hand to prove that the abdominal sympathetic system contains nerves of this kind.² It is also possible to incite dilator effects in the domain of the *nervi erigentes*, by way of which the erectile tissues of the reproductive organs are reached. It must be remembered, however, that the tenseness of these organs is not caused by vasodilatation alone,

¹ Dastre and Morat, *Red. exper. sur le systeme nerv. vasomoteur*, 1884.

² Burton-Opitz, *Pflüger's Archiv*, cxiii, 1908, 553.

but also by an actual stagnation of the blood stream which results in consequence of an obstruction to the venous return. The latter effect is made possible by the contraction of circular cushions of muscular tissue which form sphincters at the points of junction between the venules and the cavernous blood spaces.

(b) The dilator and constrictor reactions may be dissociated by chemical means. Thus, it has been found by Dale¹ that ergotoxin possesses the property of paralyzing the constrictor mechanism, so that the stimulation of any mixed vasomotor nerve must give way in time to dilatation. It is also possible to produce vasomotor effects solely with the aid of chemical agents so that we need not resort to the electrical stimulation of a nerve. For example, adrenalin in very small doses dilates the blood-vessels of the cutaneous circuits, while larger doses give rise to a constriction.² In the same way, it has been found that proteoses cause a dilatation, while chrysotoxin (ergot) stimulates the constrictor mechanism.

(c) The constrictor and dilator reactions may also be dissociated by changing the temperature or by changing the frequency of the stimulation. Thus, Howell, Budget and Leonard³ have shown that the irritability of the dilator fibers of the sciatic nerve may be destroyed sooner than that of the constrictors by simply heating or cooling the nerve. If a quickly interrupted current of moderate strength is applied to a nerve, the usual result is vasoconstriction. Bowditch and Warren,⁴ however, have found that infrequent electrical stimuli commonly give rise to a dilatation instead of a constriction. In the case of the renal blood-vessels, Bradford⁵ employed fifty induction shocks at intervals of one second. Very similar results have been obtained with the greater splanchnic nerve, by Meltzer and Auer,⁶ and Burton-Opitz.⁷ The infrequent excitation of the central end of this nerve gave rise to reflex vasodilatation and a most pronounced fall in blood pressure. It might also be mentioned that the degeneration following the division of the sciatic nerve, affects the constrictor fibers first of all, so that vasodilator effects may be obtained for some time after its constrictor power has been lost.

The Results of the Reaction.—In general, it holds true that the division of a nerve containing vasomotor fibers is followed by a relaxation of the blood-vessels innervated by it. The vascular area so affected loses its tonic resistance and becomes engorged with blood and distinctly warm to the touch. If this area is sufficiently large, these changes must, of course, react upon the general circulation and produce a fall in the general pressure, because a considerable quantity of the systemic blood must find its way into these relaxed vessels. In many cases these blood-vessels regain their tonus within a comparatively brief period of time, provided, of course, that they are still in connection with ganglionic elements. The latter are capable of assuming the function of those chief centers with which they were previously connected. This is especially true of the blood-vessels situated in the realm of the sympathetic system, because this system embraces numerous local conglomerations of ganglion cells which are markedly independent in their function from the cerebrospinal structures.

Most generally, the excitation of the distal end of a divided vaso-

¹ Jour. of Physiol., xlv, 1913, 291.

² Hartman, Am. Jour. of Physiol., xxxviii, 1915, 438.

³ Jour. of Physiol., xvi, 1894, 298.

⁴ Ibid., vii, 1886, 416.

⁵ Ibid., x, 1889, 358.

⁶ Centralb. für Physiol., 1916.

⁷ Am. Jour. of Physiol., xlii, 1917, 498.

motor nerve with currents of medium strength and frequency gives rise to a vasoconstriction in the part innervated by it. This result may also be obtained by stimulation of the intact nerve, and naturally, if a certain nerve is composed solely of dilator fibers, its excitation must be followed by a dilatation. As an example of this kind might be mentioned the chorda tympani which, as has been stated above, consists of dilator fibers for the submaxillary and sublingual glands.

As far as the result of these constrictor reactions is concerned, it must be evident that the diminution in the caliber of the arterial terminals must reduce the arterial throughflow. This change is associated with an increase in the arterial pressure and a decrease in the capillary and venous pressures. Conversely, a vasodilatation must favor a greater escape of blood into the capillaries and occasion a fall in the arterial and a rise in the capillary and venous pressures.

It has previously been emphasized that the vasomotor mechanism is the chief factor concerned in the production of the peripheral resistance, and that the latter in turn plays a most important part in the production of blood pressure. The other three factors are the energy of the heart, the total quantity of the blood, and the elasticity of the blood-vessels. Consequently, the blood pressure must be entirely dependent upon the proper interaction of these four values. Thus, it will be seen that the effects of a vasoconstriction may be greatly lessened by a reduction in the cardiac output, while a vasodilatation may be quite offset by an augmentation of the action of the heart. This compensatory phenomenon is indeed a very common one, because a high blood pressure, resulting in the course of a general vasoconstriction, is usually neutralized by a reduction in the cardiac output. But, it may also happen that the other factors act in perfect unison with the vasomotor mechanism and thus occasion an exaggeration of the vasomotor effect. For example, if a general vasoconstriction occurs synchronously with a high cardiac rate, a rise in blood pressure must result which must greatly exceed the rise produced by the vasoconstriction alone.

Nothing further need be said regarding the pressor and depressor reactions. Inasmuch as these effects are brought about reflexly by impulses generated in different parts of the body, the vasomotor center must be activated first before these impulses can be transferred upon the efferent channels. One or the other of these effects may be elicited either by stimulating the afferent nerve while intact, or by dividing it and using its central end for the stimulation. Obviously, if the distal end of a nerve of this kind is subjected to the excitation, the impulses here generated cannot reach the center at all and hence, no pressor or depressor effect can be evoked. As a typical example of a depressor nerve might be mentioned the depressor cordis, the stimulation of which produces a general reflex vasodilatation and a most decided fall in blood pressure. Similar results may be obtained by the excitation of the splanchnic nerve, and especially if currents of

low strength and frequency are employed. In fact, pressor and depressor fibers are contained in many nerves, such as the sciatic and the vagus, but their presence can only be detected by the stimulation of the central ends of these nerves and by the use of infrequent shocks of low intensity.

Methods Used to Detect Vasomotor Action.—While it has been possible to prove histologically that the walls of the blood-vessels contain nervous structures, this fact in itself is not sufficient to show that they are in possession of vasomotor elements. In other words, the only definite proof of vasomotor activity is to be found in the occurrence of the reaction itself. We may resort to *inspection*, because if all indirect factors, such as external pressure, have been ruled out, the blanching of a part may justly be referred to a vasoconstriction and its reddening to a vasodilatation. These alterations in the vascularity are usually associated with changes in *temperature*, a vasoconstriction occasioning a fall and a vasodilatation a rise in the temperature of the part. Probably the most direct proof of vasomotor activity may be obtained with the help of the recording *stromuhr*, this instrument being inserted in the artery or vein of the part to be experimented upon. As has been stated above, this instrument registers the volume of the blood stream and may therefore be used to see whether or no the flow is affected by the excitation of nerves and other experimental procedures. A decrease in the arterial supply would then betray a constrictor action, and an increase a dilator effect. It is also permissible to detect these vasomotor changes by making a simultaneous record of the *pressure* in the artery and vein of the organ to be examined. A mercurial manometer and water manometer are employed for this purpose. Clearly, a rise in the arterial and a fall in the venous pressure would betray a vasoconstriction, and a fall in the arterial and a rise in the venous pressure, a vasodilatation. These changes are easily explained, because the former reaction must increase and the latter decrease the resistance to the arterial throughflow. The manometer is also used to detect vasomotor effects of a more general kind. It is then connected with one of the principal arteries, such as the carotid or femoral. A rise in the general pressure may then be attributed to a constriction of an extensive area of the circulatory system, and a fall in the general pressure to a vasodilatation of rather wide extent. Lastly, it is possible to place the organ to be experimented upon in a *plethysmograph*. Under this condition a diminution in the volume of the organ would point toward a vasoconstriction, and an increase in its volume toward a vasodilatation. But naturally, if these procedures are practised, care must be taken to exclude all indirect effects, such as may be produced by a mechanical obstruction to the blood flow. An occurrence of this kind usually leads to a stagnation of the blood and an increase in the volume of the organ which can scarcely be differentiated from a true vasomotor effect.

SPECIAL VASOMOTOR REACTIONS

The Spinal Cord.—As the spinal cord is the chief highway by means of which the vasomotor center in the medulla stands in communication with the constrictor and dilator mechanisms of the blood-vessels, the destruction of this part must lead to a pronounced fall in blood pressure. The tonic influences of the higher center are then prevented from reaching the periphery, as are also those generated in the minor centers of the cord itself. In other words, a general vascular relaxation now results which may finally produce an almost complete stoppage of the blood flow. The animal, so to speak, is bled into its own highly relaxed vessels.

A fall in blood pressure may also be produced by dividing the cord either in its cervical or in its thoracic region. In both cases the blood-vessels innervated by those nervous elements which are situated posteriorly to the cut, lose their tonus and relax. It is to be noted, however, that this relaxation is not permanent, because the lower spinal centers then develop a tonic power independent of that of the rest of the cord. The blood-vessels gradually regain their former caliber and enable the blood pressure to return to a value approaching normal. From the foregoing data, it may also be inferred that the excitation of the peripheral stump of the spinal cord must give rise to a vasoconstriction and a rise in the general blood pressure, because the constriction of the formerly relaxed blood-vessels leads to the transfer of a large amount of previously stagnated blood into the general circulatory system. The stimulation of the central stump of the divided spinal cord with currents of ordinary strength sets up different reflexes which usually result in a pressor reaction.

The Sciatic Nerve.—This nerve must be considered as the vasomotor highway of the posterior extremity. In accordance with the preceding analysis, it may be gathered that its division occasions a relaxation of the blood-vessels innervated by it, but a marked reduction in the general blood pressure cannot result in consequence of this procedure, because the extra quantity of blood which finds its way into the circulatory channels of the leg, is not sufficiently large to affect the dynamic conditions in the general circulation. The stimulation of the distal stump of the divided sciatic nerve is usually followed by a constriction of the peripheral blood-vessels, the superfluous amount of blood being again driven into the general circuits of the body. But this transfer remains as a rule without decisive effect upon the general circulation for the reason just given. The result ordinarily obtained upon excitation of its central end is a rise in blood pressure, but this pressor effect may be changed into a depressor reaction by lessening the frequency and intensity of the stimuli. The foregoing account is also applicable to other spinal nerves, such as the brachial.

Our knowledge regarding the vasomotors of *skeletal muscle tissue* is still very indefinite, owing to the difficulties experienced in differ-

entiating between the nervous effects and those caused by the contracting muscle fibers. Gaskell¹ states that the excitation of the distal end of the motor nerve of the mylohyoid muscle gives rise to a dilatation which persists even after the administration of curare. Besides, the determinations of the blood supply of the gracilis muscle of dogs, which have been undertaken by Burton-Opitz² and Tschuewsky,³ have shown that the flow is greatly diminished during the period of contraction of the muscle but much increased during its relaxation. It need scarcely be emphasized that these changes may be chiefly mechanical and must occur whenever the motor nerve of a muscle is stimulated. This is shown by the fact that the tetanization of the muscle reduces the blood flow almost to zero. We have no means of differentiating between these mechanical effects and those of vasomotor origin, unless we should paralyze the motor plates by means of curare. But again, inasmuch as this agent might also affect the vasomotor terminals in muscle, it could not serve as a means to decide this question one way or another. This uncertainty regarding the existence of vasomotor nerves in muscle tissue, has not been lessened by the experiments of Kaufmann,⁴ who has ascertained that the blood flow through the masseter muscle of the horse may be increased as much as five times by permitting this animal to masticate normally. Instead of referring this change to a stimulation of the nervous mechanism, we might attribute it with equal justification to a mechanical widening of the blood-vessels. This explanation might be adhered to in spite of the fact that this action is associated with a fall in pressure in the artery supplying this muscle, and an increase in pressure in the vein draining it.

The Trigeminal Nerve.—This nerve embraces vasoconstrictor fibers for the conjunctiva, the sclerotic coat and iris of the eye, as well as for the mucous lining of the nose and gums. Its lingual branch innervates the blood-vessels of the tongue. In the rabbit, the auricularis magnus nerve, a branch of the third cervical, embraces vasomotor fibers for the ear.

The Cervical Sympathetic Nerve.—This nerve forms the connection between the inferior and superior cervical ganglia. During its course along the neck, it lies in relation with the carotid artery and the vagus nerve. In some animals, such as the rabbit, it pursues an independent course, while in others it attaches itself to the vagal fibers (cat) or becomes completely intermingled with them (dog). Distally to the superior cervical ganglion, the individual fibers follow in the path of the blood-vessels and finally attain such structures as the cerebrum, the ear, submaxillary gland, larynx, thyroid body, and the integument of the head.

¹ Jour. of Physiol., i, 1878, 108.

² Am. Jour. of Physiol., ix, 1902, 161.

³ Pfüger's Archiv, xcvi, 1903, 289.

⁴ Arch. de Physiol. et Path., 1892.

One of the most striking vasomotor reactions obtainable with the aid of this nerve is the following: If the blood-vessels in the ear of a rabbit are rendered more clearly perceptible by transillumination, it can readily be observed that the division of this nerve occasions a very decided vascular relaxation. Many blood-vessels which were previously quite invisible to the naked eye, are now sharply outlined, and the ear on the operated side is distinctly warmer than the one on the normal side. If the distal (cephalic) end of this nerve is stimulated, a vasoconstriction soon results which betrays itself most unmistakably by a diminution in the caliber of the central artery and its principal branches. These vessels grow smaller and smaller until they can

FIG. 223.—THE VASOMOTOR REACTIONS IN THE EAR OF THE RABBIT ON DIVISION AND STIMULATION OF THE CERVICAL SYMPATHETIC NERVE.

A. Normal. B. After division of the cervical sympathetic nerve. C. On stimulation of the distal end of the divided cervical sympathetic nerve.

scarcely be made out. The veins remain visible for a much longer time, but eventually collapse owing to the cessation of the arterial influx. This ear now feels distinctly colder than the one on the normal side. On discontinuing the stimulation, the arteries again relax until they have attained their former caliber. These changes may be produced again and again, but naturally, only at intervals, to avoid fatiguing this vasomotor mechanism.

The superior cervical ganglion also serves as the distributing center of the sympathetic fibers to the *sublingual* and *submaxillary glands*. These fibers follow in the course of the art. glandularis submaxillaris. The aforesaid organs also receive a second nerve supply which is derived from the bulbar autonomic system and appears peripherally in the form of a small nerve known as the *chorda tympani*. The latter leaves the system of the facial nerve and attaches itself at first to the lingual nerve of the fifth system. When it reaches the region of Whar-

ton's duct, it turns abruptly and attains the aforesaid glands by way of this duct. Under ordinary conditions of experimentation, these two sets of fibers possess an antagonistic action upon the vascularity of these glands, because the cerebral nerve or chorda tympani possesses vasodilator and the sympathetic nerve vasoconstrictor qualities. The former change is associated with a secretion of a large quantity of very watery saliva, and the latter with a scanty production of a very viscous and turbid saliva.¹

These changes may be studied most advantageously in a dog or large cat. The stimulation of the chorda is undertaken as a rule in the triangle where this nerve leaves the lingual to attach itself to Wharton's duct. The excitation of the sympathetic may be accomplished at any point of its course along the neck, but as the vagal and sympathetic fibers of the dog intermingle, it becomes necessary to apply in this case the electrodes to the distal (cephalic) end of this nerve. It should be

FIG. 224.—SCHEMA ILLUSTRATING THE NERVE SUPPLY OF THE SUBMAXILLARY GLAND.

SG, submaxillary gland; supplied by a small artery from the carotid system (CA). It is drained by a small vein which generally enters the facial (FV) at its point of confluence with the lingual vein (LV). The external (ESV) and internal (JSV) maxillary veins invest the gland and unite to form the external jugular vein (EJV). The sympathetic nerve supply is derived from the sup. cerv. ganglion (SCG). The chorda tympani (CT) attaches itself to the lingual nerve LN and then to Wharton's duct (W); S, lower jaw.

remembered, however, that we are concerned at this time solely with the aforesaid vascular reaction and not with any other effect which this stimulation might produce. In the cat, it is possible to isolate the sympathetic fibers from the vagus proper, because their line of contact is clearly marked by a small blood-vessel. If the surface of the submaxillary gland is now fully exposed to the view, it will be seen that the stimulation of the chorda causes it to redden, while the excitation of the (vago-) sympathetic causes it to pale. These changes in the vascularity of this organ may also be made out manometrically, or, as has been done by Burton-Opitz,² by means of the stromuhr inserted in the distal end of the external jugular vein. In the latter case, however, all tributary veins must first be ligated in such a manner that solely the blood from the submaxillary gland is enabled to enter

¹ Heidenhain in Hermann's Handb. der Physiologie, v, 1883.

² Jour. of Physiol., xxx, 1903, 132.

this instrument. Quite naturally, the excitation of the chorda tympani then gives rise to an augmentation of the venous pressure and flow, because the resulting vasodilatation allows a greater quantity of arterial blood to pass through this gland. The stimulation of the sympathetic, on the other hand, then leads to a diminution in the venous pressure and flow, because the vasoconstriction immediately following, serves to place a greater resistance in the path of the arterial blood.

The superior cervical ganglion is also connected by postganglionic fibers with the blood-vessels of the brain. This fact has been demonstrated by Jenson¹ who has measured the venous return from this organ with the aid of a stromuhr inserted in the external jugular vein. Under this condition, the stimulation of the distal end of the cervical sympathetic nerve invariably led to a diminution in the blood flow through this vein. The fact, that the cerebral blood-vessels are equipped with vasoconstrictor powers, has also been established by Wiggers,² who measured the quantity of fluid perfused through the blood-vessels of an excised brain before and during the administration of adrenalin. Very similar reductions in the cerebral blood-supply have also been incited by the direct stimulation of the internal carotid artery at the point where it enters the skull. It is entirely probable that the constrictor fibers follow this artery in their course to intracranial parts. Less convincing are the results obtained with the help of the plethysmograph, but several observers (Weber) claim to have noted certain variations in the volume of the brain which could not be explained in any other way than by assuming that this organ is innervated by constrictor and dilator fibers.

The Greater Splanchnic Nerve.—This nerve embraces those fibers of the thoracic outpouring of sympathetic fibers which are destined to regulate the caliber of the blood-vessels of the abdominal organs, inclusive of the kidneys, adrenal bodies, stomach, intestine, liver, pancreas and spleen. These organs, which are commonly called the splanchnic organs, are not reached by them directly but only by way of several relay stations forming the so-called solar plexus. The latter embraces the right and left suprarenal, and the mesenteric and celiac ganglia. The connection between these and the organs just enumerated, is effected by several postganglionic paths, such as the renal, mesenteric, splenic, celiac and hepatic plexuses.

The point to be especially emphasized at this time is that these nerves control the blood supply of extremely large and vascular structures and possess, therefore, an almost dominating influence upon the distribution of the total quantity of the circulating blood. This statement can be substantiated by the following simple experiment. If the general blood pressure is recorded by means of a mercurial manometer connected with the carotid artery, it will be seen that the di-

¹ Pflüger's Archiv., ciii, 1904, 195.

² Am. Jour. of Physiol., xiv, 1905, and xxi, 1908.

vision of the right or left splanchnic nerve leads in the course of a few moments to a marked diminution in the pressure. This effect may be rendered even more conspicuous by dividing both nerves. If the distal (abdominal) end of this nerve is now stimulated with a current of moderate strength and duration, it will be noted that the systemic blood pressure rises rather abruptly and remains high for some time after the cessation of the stimulation. All vasomotor reactions, however, develop slowly, for the reason that smooth muscle cells do not contract so rapidly as the striped variety. Neither is it possible to continue an experiment of this kind for any considerable length of time, because it is eventually cut short by fatigue. It has been mentioned above that the excitation of the central (thoracic)

FIG. 225.—RECORD OF THE CAROTID BLOOD-PRESSURE IN RABBIT DURING STIMULATION OF THE LEFT GREATER SPLANCHNIC NERVE.

end of this nerve with currents of low frequency and strength gives rise to a general vasodilatation and fall in the systemic blood pressure.

In explaining this reaction it should be borne in mind that the division of the splanchnic nerve is soon followed by a relaxation of the blood-vessels innervated by it. Consequently, a steadily increasing quantity of blood must leave the systemic channels and become lodged in those of the splanchnic organs. In some animals, this transfer of blood may lead to circulatory disturbances which actually endanger their life. At all events, the fall in general pressure resulting from the engorgement of the splanchnic blood-vessels, eventually gives rise to cerebral anemia and various symptoms, such as vertigo, mental lethargy and muscular weakness. Conditions constantly arise in our system which require extra amounts of blood to be transferred from place to place and especially when the digestive organs are actively engaged in reducing and absorbing the food. This means that they must be supplied with larger quantities of blood which, on being with-

drawn from the systemic circuit, generally give rise to mental and bodily fatigue. These symptoms are also observed whenever the tonicity of the splanchnic blood-vessels is lost in consequence of general nervous debility, irritation of the intestines, and other conditions.

Concurrently, it may be gathered that the stimulation of the distal end of the greater splanchnic nerve must occasion a transfer of blood from the splanchnic area into the general circulation, because the vasoconstriction resulting in consequence of this procedure, forces a large quantity of blood out of these channels into the veins and the general circuit and prevents at the same time a corresponding influx of arterial blood. The systemic blood pressure, therefore, is rapidly increased, but naturally, this augmentation cannot exceed physiological limits, because while the arterial blood does not find free access to the splanchnic organs, it is still in a position to leave the arterial channels by way of the carotid and femoral arteries.¹ Thus, while the stimulation of the splanchnic nerve lessens the flow through the organs innervated by it,² the circulatory conditions in the central venous system remain practically unaltered.

The Depressor Nerve.—The function of this nerve has been described in detail in one of the preceding chapters (page 329). It is a sensory nerve and conducts impulses from the heart to the cardiac and vasomotor centers. Its function is to produce a general reflex vasodilatation, and therefore a fall in the systemic blood pressure. In the nature of things, this effect can only be obtained by the stimulation of either the intact nerve or of its central or cephalic stump. It has been stated above that marked depressor effects may also be obtained with the help of the thoracic sympathetic nerve and its branches.

CHAPTER XXXV

THE CIRCULATION THROUGH SPECIAL ORGANS

A. THE CORONARY CIRCULATION

In man the orifice of the *right coronary artery* is situated in the anterior sinus of Valsalva, whence this blood-vessel passes forward and follows the right auriculoventricular groove until it reaches the interventricular groove. At this point it divides into two branches, the smaller of which continues onward in the left auriculoventricular groove, and the larger in the inferior interventricular groove. The *left coronary artery* arises from the left fossa of Valsalva and, passing backward, divides at the left auricular appendix into two branches,

¹ Edwards, Am. Jour. of Physiol., xxxv, 1914, 15.

² Burton-Opitz, Quart. Jour. of Exp. Physiol., iv, 1912, 83.

one of which descends along the anterior interventricular groove to the apex of the heart, while the other follows the left auriculoventricular groove. From these superficial blood-vessels, forming what is known as the *extramural system*, branches are given off which penetrate the substance of the heart and by repeated division give rise to the so-called *intramural system*.

The cardiac veins follow in the course of the arteries, uniting eventually in the coronary sinus which is about one inch in length and occupies the inferior extremity of the left auriculoventricular groove. It empties into the right auricle in front of the inferior caval opening, its orifice being guarded by the valve of Thebesius.

In this connection it should be recalled that the hearts of those lower forms, which are not in possession of an independent circulation, obtain their nutritive material directly from the blood as it traverses the cardiac chambers. Many of these organs also contain irregular tubular passages which penetrate the musculature and thus enable the blood to come into contact with even the most remote cells. A similar arrangement is present in the mammalian heart. Numerous openings, the so-called foramina of Thebesius, establish a communication with a system of tubules which ramify below the endocardial membrane,¹ but the nourishment which the mammalian heart is able to derive from this source is not sufficient for its metabolic requirements.²

That the activity of the mammalian heart is actually dependent upon the coronary blood supply, may readily be gathered from the fact that an isolated and quiescent organ may be made to beat again by instituting an artificial circulation through its coronary circuit. In fact, the frequency and force of the cardiac contractions invariably go hand in hand with the pressure under which the perfusion is made. Very similar results may be obtained at times with the heart of the cat. Thus, if its aortic orifice is occluded, it ceases to beat almost immediately, but may be made to contract again by filling its chambers with defibrinated blood under a pressure of about 75 mm. Hg. This procedure, however, is not so reliable as the perfusion through the coronary artery. This fact, that it resumes its activity under these circumstances, might also be explained upon the basis that the cat's heart possesses a more extensive system of direct nutritive channels than that of other mammals. The ligation of the coronary arteries in the dog is followed almost immediately by a diminution in the rate and force of the heart beat and eventually by a complete stoppage. In fact, Parker has shown that the occlusion of one of its branches, namely the circumflex artery, suffices to arrest the heart in about 80 per cent. of the animals.

While the superficial cardiac vessels are protected in a measure by the visceral layer of the pericardium, as well as by connective tissue and fat, the deeper branches are directly exposed to the power

¹ Pratt, Am. Jour. of Physiol., i, 1898, 86.

² Langendorff, Pflüger's Archiv, lxi, 1895, 291.

of the musculature. It need not surprise us, therefore, to find that the mechanical influences thus exerted upon the blood stream play an important part in the flow through this system of vessels. In fact, much uncertainty has always prevailed regarding the manner and the time during which the coronary blood-vessels are filled. Brücke,¹ for example, has expressed the idea that the heart possesses a self-regulatory mechanism whereby the circulation through this organ is made to differ in certain particulars from that through other parts of the body. As the orifices of the coronary arteries are situated behind the flaps of the aortic valve, the claim has been made that these openings are completely closed during each ventricular systole² and that the heart obtains its supply of blood only during the diastolic period when these valve flaps are in the position of closure. This mode of filling seemed the more likely, because the relaxation of the cardiac muscle must exert a favorable influence upon the influx of the aortic blood, while its contraction must force the blood onward into the veins and right auricle.

This view, however, has found no substantiation, because it has been proved by Martin and Sedgwick,³ as well as by Porter,⁴ that the pressure changes in the coronary arteries coincide very closely with those occurring in the systemic circuit. Moreover, Rebatal⁵ has shown that the coronary blood flow suffers an acceleration at the beginning of each systole, but ceases as soon as the musculature has attained a state of maximal contraction. A second augmentation in the flow is said to result during diastole which, however, soon suffers a retardation in consequence of the gradual filling of the right auricle. These data prove, on the one hand, that the coronary circuit remains in free communication with the aorta even during the systole of the heart and, on the other, that the contracting musculature exerts a powerful pressure upon the intramural blood-vessels which greatly favors their emptying. In further substantiation of this statement it might be mentioned that if a piece of ventricle is made to beat rhythmically by perfusing it with a nutritive fluid through its artery, a jet of blood is forced from the distal venous orifice with every contraction (Porter).

The question whether the coronary circuit is equipped with a vasomotor mechanism has not been decided as yet, because any attempt to solve this problem, either by measuring the blood flow directly or by determining the changes in pressure, must be seriously hampered by the mechanical action of the contracting musculature. Neither is it possible to obtain more accurate data by stimulation of the efferent nerves of the heart, because the vagal and sympathetic

¹ Der Verschluss der Kranzschlagadern durch die Aorten Klappen, Wien, 1855.

² A statement generally attributed to Thebesius (1708).

³ Jour. of Physiol., iii, 1880, 165.

⁴ Am. Jour. of Physiol., i, 1898, 71.

⁵ Dissertation, Paris, 1872.

fibers modify the rate and force of the heart in such a degree that it becomes quite impossible to recognize pure vasomotor changes. For this reason, much stress cannot be placed upon the experiments of Parker¹ and Maas² who measured the outflow from the coronary veins of isolated hearts of cats while these organs were being perfused through their coronary arteries. Under these conditions, the excitation of the vagus led to a diminution and the stimulation of the sympathetic fibers to an increase in the flow. In accordance with the foregoing statement, we are not justified in attributing the former effect to a vasoconstriction and the latter to a vasodilatation.

For the same reason no definite conclusions can be drawn from the observations of N. Martin,³ showing that the stimulation of the vagus produces an enlargement of the smaller blood-vessels situated in the surface layers of the heart and that a dilatation of these channels results early during the state of asphyxia, when the general blood pressure preserves as yet a perfectly normal value. Schäfer,⁴ as well as Wiggers,⁵ is of the opinion that the changes following the stimulation of the cardiac nerves during perfusion may be explained more satisfactorily by attributing them to other than vasomotor influences. It has been reported, however, that the coronary vessels of the quiescent heart constrict in response to adrenalin, and that this agent increases the flow through this organ by modifying the character of its contractions.

B. THE PULMONARY CIRCULATION⁶

The dynamical factors which are responsible for the flow of the blood through the lesser circuit, present the same general characteristics as those previously discussed in connection with the greater circuit. The pressure in the pulmonary artery finds its origin in the activity of the right ventricle. As the driving force developed by this chamber is relatively slight, it cannot surprise us to find that the entire pulmonary circulation is carried on with the aid of a rather low pressure and, hence, with a lesser expenditure of energy, than the systemic. But this statement is not meant to imply that the pulmonary circulation is less effective, but merely to suggest that the low pressures here prevailing, are made possible by the fact that the resistance in this circuit is very slight. That this deduction is correct may be gathered from the observation that the pulmonary arterioles possess a larger caliber and are equipped with only a scanty amount of smooth muscle tissue.

The blood-vessels of the lungs are constantly undergoing passive

¹ Boston Med. and Surg. Jour., 1896.

² Pflüger's Archiv, lxxiv, 1899, 281; also see: Dogiel and Archangelski, *ibid.*, cxvi, 1907, 482.

³ Transact., Med. and Chir. Fac. of Maryland, 1891.

⁴ Arch. des sciences biol., xi, Suppl., 1899.

⁵ Am. Jour. of Physiol., xxiv, 1909, 391.

⁶ Discovered by Servet and Columbo during the middle of the 16th century.

variations in their caliber in consequence of the respiratory movements of the thorax. They are widened during normal inspiration and compressed during expiration. This leads us to infer that the through flow is greatest during the former phase, because the resistance is least at this time. But if the lungs are distended artificially through the trachea, these conditions are reversed, because their inflation with air produces a compression of their blood-vessels. The peripheral resistance is increased during the inflation. Conversely, it may be concluded that the deflation of these organs enables the vessels to acquire their previous caliber. This change is associated with a diminution in the peripheral resistance.¹ As has previously been noted, these rhythmic variations in the conditions inside the thorax play an important part in the production of the respiratory oscillations in blood pressure. Attention should also be called at this time to the fact that the vascularity of the lungs is subject to the conditions prevailing in the heart. Any momentary excess in the venous influx must, of course, be accommodated by the distended pulmonary channels until the heart is again capable of propelling it. A hyperemia of a more permanent kind, however, must result whenever the left ventricle is unable to relieve the lungs of a normal quantity of blood. A condition of the kind must arise during stenosis or regurgitation of the mitral or aortic valves. The lesser circuit, therefore, is capable of acting as a reservoir, the purpose of which is to equalize the flow through the heart.

The measurements of the pressure and flow in the pulmonary artery meet with serious difficulties, because the insertion of a cannula in this blood-vessel or in any of its branches necessitates in many animals the opening of the pleuræ and a temporary blocking of the pulmonary circulation. In rabbits, however, it is possible to gain free access to the heart by simply dividing the sternum in the median line.² As the pleural sacs do not quite reach to this line, they need not be opened and artificial respiration need not be resorted to. Beutner³ has given the following values which have not been materially changed in more recent years:

Dog.....	28-31 mm. Hg
Cat.....	15-19 mm. Hg
Rabbit.....	9-17 mm. Hg

These figures harmonize completely with the fact that the right ventricle develops much lower pressures than the left, without, however, causing the usual systolic-diastolic differences to disappear. But as the latter show oscillations of only about 15 mm. Hg, as against 30-40 mm. Hg in the systemic circuit, their range is rather limited. In

¹ Tigerstedt, *Ergebnisse der Physiol.*, ii, 2, 1903; also see: Burton-Opitz, *Am. Jour. of Physiol.*, xxxvi, 1914, 64.

² Knoll, *Sitzungsber., Ak.*, Wien, xevii, 207, 1888.

³ *Zeitschr. für rat. Med.*, N. F., ii, Ser., 1882; also see: Bradford and Dean, *Proc. Royal Soc., London*, 1889, and Schäfer, *Quart. Jour. of Exp. Physiol.*, xii, 1919, 133.

general, therefore, it may be said that the pressure in the pulmonary blood-vessels is retained at a more constant height, amounting to about one-fifth of that generally obtained in such arteries as the carotid and femoral.

In this connection it should be remembered that the heart and large vessels are not fully exposed to the atmospheric pressure, but to the atmospheric pressure less the elastic pull or recoil of the lungs. Furthermore, this force must be of greater consequence in the case of the soft veins than in that of the more solidly built arteries. With the glottis opened, the respiratory surface of the lungs is, of course, fully exposed to the atmospheric pressure. In the second place, it should be remembered that the inspiratory movements increase this negative pressure in the thorax and tend, therefore, to augment the aspiratory action upon the central blood-vessels. This accounts for the fact that the pulmonary vessels are more fully dilated during inspiration and offer at this time a lesser resistance to the through flow of the blood.¹

The velocity of the flow through the lungs is much greater than that through the vessels of the systemic circuit. It has been found that about one-fifth of the total circulation-time is used up in the passage of the blood through this organ. Stewart,² for example, has shown that the average time required by the blood to complete its journey from the right to the left side of the heart, amounts to 8.7 seconds in a dog weighing about 12 kg. and to 10.4 seconds in a dog weighing about 18 kg. If applied to man, these figures indicate that the circulation-time for the pulmonary circuit is about 15 seconds.

The existence of vasomotors in the lungs is still an open question, because their recognition is made difficult by the fact that satisfactory test conditions cannot easily be established. Whether the animal be made to respire normally (rabbit) or artificially (dog), the constant mechanical action of the lungs upon the blood-vessels must necessarily tend to destroy any variations in the pressure and flow of a true vasomotor kind. Furthermore, this difficulty cannot be overcome by keeping the lungs distended with a constant current of air, nor is it possible to improve the experimental conditions by perfusing the quiescent organs with a nutritive fluid. In either case, the pulmonary circulation cannot be considered as being carried on under conditions at all comparable to normal.

The foregoing statement explains in a way the diversity of the results obtained. Bradford and Dean,³ for example, have decided in favor of the existence of pulmonary vasomotors, their conclusions being based upon differential records of the blood pressure in the carotid and pulmonary arteries during stimulation of the third, fourth and

¹ DeJager, Pfüger's Archiv, xxvii-xxxix, 1879-1886.

² Jour. of Physiol., xv, 1894, 1.

³ Ibid., xvi, 1894, 34.

fifth thoracic spinal nerves. Brodie and Dixon,¹ on the other hand, deny their presence, and state that the excitation of the vagus or sympathetic nerve does not cause a significant alteration in the rate of perfusion through an isolated lung. Similar results have been obtained by Burton-Opitz,² who measured the blood flow in the pulmonary artery with the aid of the stromuhr. The use of adrenalin has failed to decide this matter one way or another. In the hands of the investigators just named, this agent has given negative results, while Plumier³ has found that the flow through a perfused lung may be diminished by adrenalin. A diminution in the flow is also said to follow the stimulation of those sympathetic fibers which pass between the first thoracic ganglion and the pulmonary plexus. It is conceded, however, that the changes so obtained are slight and not absolutely constant. This result serves as an argument against an active behavior of the pulmonary blood-vessels, because true vasomotor reactions are always of an amplitude which makes the use of very delicate means for their detection superfluous.

C. THE PORTAL AND RENAL CIRCULATIONS

The portal system embraces those abdominal organs which drain their blood into the *vena portæ*, a large venous tube formed by the union of the *venæ mesentericæ* and the *vena gastrolienalis*. Before this channel enters the hilus of the liver it receives another vein of considerable size, namely the *vena pancreatica*. Centrally to the liver, the blood is conducted into the inferior *vena cava* by the hepatic veins. As the name indicates, the mesenteric veins return the blood from the intestines, while the gastrolienalis collects it from the spleen and the largest part (left) of the stomach. The remaining portions of this organ, as well as the principal mass of the pancreas and the middle and upper segments of the duodenum, are drained by the pancreatic vein.⁴

The arterial supply of these organs is obtained first of all from the *celiac axis* which divides into three branches, namely: (a) the *hepatic artery* which supplies the framework of the liver, the body of the pancreas, and the adjacent portion of the duodenum, (b) the *gastric artery* which ramifies upon the right expanse of the stomach, and (c) the *splenic artery* which passes to the spleen, the cauda of the pancreas and the neighboring left segment of the stomach. The intestine receives its blood from the *superior and inferior mesenteric arteries*.

The organs just enumerated are innervated, on the one hand, by the vagi nerves and, on the other, by the greater and lesser splanchnic nerves. The former terminate in the region of the gastro-esophageal

¹ Jour. of Physiol., xxx, 1904, 476.

² Proc. Soc. of Exp. Med. and Biology, 1904.

³ Jour. de physiol. et de pathol. generale, vi, 1904.

⁴ This description applies to the dog. More complete data may be obtained from Ellenberger and Baum's Anatomie des Hundes, Berlin, 1891.

junction, where the united ventral vagus forms the plexus gastricus anterior, and the dorsal vagus, the plexus gastricus posterior. Both plexuses are intimately connected with one another by fibers and communicate with the abdominal ganglia of the sympathetic system by direct rami to the plexus suprarenalis. The plexus gastricus ventralis also gives off fibers which pass along the lesser curvature of the stomach and eventually ramify upon the pylorus where they unite with the plexus hepaticus.

It is a well-known fact that the *vagi nerves* convey musculo-motor and sensory impulses to and from the stomach and the other organs of the abdomen.¹ They do not, however, seem to possess a true vasomotor function. It should be mentioned at this time that the excitation of the vagus frequently produces very decided reductions in the blood supply of the stomach and intestine, which are not due to the inhibition of the heart nor to an active constriction of the blood-vessels, but are dependent upon the peristaltic motion invariably elicited by the stimulation of this nerve. The influence of the inhibitor action of the vagus upon the heart and blood flow may be avoided by simply stimulating this nerve at any point below this organ or by administering an adequate amount of atropine to paralyze the inhibitor mechanism. The perseverance of these vascular changes, even after these precautionary measures have been taken, must lead us to conclude that the contraction of the gastric and intestinal walls lessens the size of the blood-bed and thus diminishes the blood flow in a perfectly mechanical manner.

The *vagi*, however, form a most important afferent path by means of which the organs of the abdomen are connected with the central nervous system. They are concerned, therefore, with the production of numerous reflex actions, such as (a) the inhibition of the heart² in consequence of strokes upon the region of the stomach (plexus solaris), (b) the systemic vasomotor and cardiac disturbances occasioned by chemical and mechanical irritation of the intestine, (c) the referred symptoms accompanying inflammatory reactions in any part of the abdominal cavity, and others.

Like the *vagi*, the *splanchnic nerves* are efferent and afferent in their function. They form the connection between the thoracic and abdominal ganglia of the sympathetic system. Beginning at the ganglion stellatum, a number of fibers pass downward along the spinal column to be constantly augmented by fibers derived from the different spinal nerves (Fig. 226). Opposite the thirteenth root, this nerve, which is known as the thoracic sympathetic, divides into the splanchnicus major and the sympatheticus abdominalis. The former pierces the diaphragm and passes toward the adrenal body, where it ramifies extensively, forming here the so-called plexus suprarenalis. The lat-

¹ Burton-Opitz, Pflüger's Archiv, cxxxv, 1910, 205.

² As we are here concerned solely with reflexes upon the circulatory system, the accompanying inhibition of the respiratory action is not considered at this time.

ter, on the other hand, continues to pursue a course along the spinal column where it soon receives branches from the lumbar portion of the spinal cord. Their points of union are marked by the lumbar ganglia. The first three of these give rise to the splanchnici minores, which pass directly across toward the suprarenal plexus. The abdominal sympathetic continues downward and eventually connects with the sacral nerves and the sympathetic system of the pelvis.

The left and right suprarenal plexuses, therefore, may be regarded as the outposts of the abdominal sympathetic system. In addition to these two plexuses, the latter includes the more centrally situated ganglion mesentericum superior and the ganglion celiacum. All these ganglia together with their extensive network of fibers and a few

FIG. 226.—DIAGRAMMATIC REPRESENTATION OF THE SPLANCHNIC SYSTEM (SOLAR PLEXUS).

T, thoracic sympathetic nerve divides into (*S*) greater splanchnic nerve and (*A*), abd. symp. nerve. The former ends in the suprarenal plexus (*B*) and the latter in the lumbar ganglia (*LG*). From the lumbar ganglia the three minor splanchnic nerves pass to the suprarenal plexus. *M*, Superior mesenteric and *C* celiac ganglia of the solar plexus. The plexuses leading out from here are: *I*, renal plexus to kidney (*K*); *II*, mesenteric plexus to intestine (*J*); *III*, hepatic plexus to liver (*L*) stomach (*St*), pancreas (*P*) and duodenum (*D*). *IV*, gastro-splenic plexus to spleen (*Sp*) and stomach (*St*); *Di*, line of diaphragm.

scattered small ganglia, form the so-called plexus solaris. Thus, the splanchnic nerves constitute the preganglionic paths and the different nerves which connect the solar plexus with the aforesaid organs of the abdomen, the postganglionic paths.

The Vasomotors of the Kidneys and Suprarenal Bodies.—These organs do not belong to the portal system, because their blood is drained directly into the inferior vena cava, but as they are innervated by the splanchnic nerves, they may be conveniently included in this discussion. In fact, it is customary to speak of those organs which derive their nerve supply from the splanchnic nerves, as forming the splanchnic system. This includes the portal organs, kidneys and suprarenal bodies. Each kidney is innervated by fibers which are derived from the suprarenal plexus and reach this organ by following the highway of the renal artery. They form the so-called plexus

renalis, which in turn communicates with the mesenteric ganglion. By measuring the blood-supply of this organ with the aid of the stromuhr, Burton-Opitz¹ has shown that the stimulation of this plexus, or of single nerves thereof, leads to a constriction of its blood-vessels and therefore to a diminution in its vascularity. This plexus also contains dilator fibers. The same results may be obtained by the excitation of the greater splanchnic nerve of the same side or, as Bradford² has shown, by the stimulation of the fibers emerging from the tenth to the thirteenth spinal nerves (dog). This investigator also states that the kidney receives dilator fibers which are derived from the eleventh, twelfth and thirteenth thoracic spinal nerves.

By cutting the renal plexus the kidney is converted into a passive organ. The renal blood-vessels relax and permit a greater quantity of blood to enter this organ; moreover, this augmentation becomes the more pronounced, the greater the arterial blood pressure. Thus, the vascularity of a denervated kidney can be increased very readily by the stimulation of either splanchnic nerve, because, as we have seen, the ensuing constriction of the portal blood-vessels raises the systemic blood pressure and, hence, also the arterial influx into this now non-resistant organ. The stimulation of the central end of the divided renal plexus usually gives rise to a reflex increase in the general blood pressure (pressor action), whereas weak and infrequent stimuli generally produce a reflex vasodilatation (depressor action). It should also be remembered that the innervation of the kidneys is unilateral.³

That the splanchnic nerves are capable of exerting a true vasomotor influence upon the adrenal bodies has not been thoroughly established.⁴ Certain evidence, however, has been presented by Elliott⁵ and Von Anrep⁶ to show that they govern the secretory activity of these glands. Thus it was found that the stimulation of the aforesaid nerves gives rise to an immediate outpouring of adrenin into the venæ suprarenales, whence this product reaches the general arterial circulation by way of the inferior cava. Here it incites its characteristic reaction consisting in a general vasoconstriction. The time which elapses between the moment of the stimulation of the splanchnic nerve and the beginning of this vasomotor reaction, amounts to about 12 to 15 seconds, in a dog weighing about 15 kg.

This outpouring of adrenal substance is a constant physiological process, tending to preserve the vasomotor tonus and to cause temporary increases in blood pressure. Keeping this fact clearly in mind, we are now in a position to consider more fully the influence which the stimulation of the splanchnic nerve exerts upon the general blood

¹ Pfüger's Archiv, cxxiii, 1908, 553.

² Jour. of Physiol., x, 1889, 358.

³ Burton-Opitz, Am. Jour. of Physiol., xl, 1916, 437.

⁴ Biedl, Pfüger's Archiv, lxxvii, 1897, 433; also: Burton-Opitz and Edwards, Am. Jour. of Physiol., xliii, 1917, 408.

⁵ Jour. of Physiol., xlv, 1912, 374.

⁶ Ibid., xlv, 1912, 307.

pressure as well as upon the blood flow through the kidneys. We have just seen that the excitation of this nerve leads not only to a constriction of the blood-vessels in the corresponding kidney, but also to a liberation of an extra amount of adrenin from the neighboring suprarenal body. As soon as this agent has reached the arterial system, a general vasoconstriction is incited which also includes the blood-vessels of the two kidneys. But, as the renal blood-vessels on the side of the stimulation have already been constricted in a direct way, the adrenin only serves the purpose of augmenting the primary effect in this particular organ. On the opposite side, on the other hand, it incites its characteristic effect. Thus, it will be seen that the stimulation of the splanchnic nerve eventually leads to a constriction of the vessels of both kidneys, but the one occurring on the side of the excitation appears almost immediately after the make of the current and is due primarily to a direct motor influence, whereas the one in the opposite organ takes place later on and is the result of the ingress of adrenin.

In the second place, we are now in a position to offer a detailed explanation of the character of the rise in the general blood pressure invariably following the stimulation of the splanchnic nerve. It has been observed by Johansson¹ that this increase does not present a single summit, but two, the initial one being somewhat smaller than the second. Elliott and Von Anrep have succeeded in showing that the second elevation is dependent upon the outpouring of adrenin, because the ligation of the suprarenal veins or the removal of the suprarenal bodies as a whole causes this summit to disappear completely. To summarize: Under ordinary experimental conditions the stimulation of the splanchnic nerve produces a vasoconstriction in the organs innervated by it. The transfer of blood associated therewith relieves the splanchnic organs of a certain quantity of blood and forces it into the general circulation. This change gives rise to the primary rise in the arterial blood pressure. Secondly, it also leads to the liberation of adrenin which, on being flushed into the arterial system, causes a general vasoconstriction which is associated with an augmentation of the constriction already produced in the splanchnic organs. In consequence of this extensive secondary involvement of the blood-vessels, the general blood pressure is again raised. The second summit of the splanchnic rise in blood pressure is therefore directly attributable to the discharge of adrenin.

The Vasomotors of the Intestines.—With the exception of the upper segment of the duodenum the intestine is innervated by fibers arising in the mesenteric ganglion of the solar plexus. These fibers pass along the mesenteric arteries. The stromuhr experiments of Burton-Opitz² have shown that the division of this postganglionic path is followed by an engorgement of the intestinal blood-vessels,

¹ Archiv für Anat. und Physiol., 1891, 103.

² Pfüger's Archiv, cxxiv, 1908, 469.

and that the stimulation of the intact plexus, or of its distal end, gives powerful vasoconstrictor effects. It has also been established that this plexus conducts afferently, because the excitation of its central stump produces a pressor reaction. The same results may be obtained by the stimulation of either splanchnic nerve; hence, the intestine is innervated bilaterally. Moreover, François-Frank and Hallion¹ claim that this preganglionic path embraces dilator fibers for this organ.

The Vasomotors of the Stomach.—These fibers ascend from the celiac ganglion of the solar plexus and follow in the paths of the three branches of the celiac axis. By measuring the venous return from this organ, Burton-Opitz² has shown that its left side, as well as the region along the greater curvature, is innervated by fibers which are derived from the plexus gastrolienalis surrounding the artery of the same name. Its pyloric portion, as well as the region of the lesser curvature, is innervated by the plexus accompanying the arteria epiploica dextra, while the pylorus proper receives its vasomotor supply by way of the plexus hepaticus and the plexus gastroduodenalis. By stimulation of the aforesaid nerves, it was possible to obtain most decided reductions in the blood supply of this organ. The same results followed the stimulation of the splanchnic nerves. The vasomotor nerves for the upper and middle segments of the duodenum are also derived from the celiac ganglion. These fibers ascend, together with those for the pylorus, by way of the hepatic plexus and the plexus gastroduodenalis.³

The Vasomotors of the Spleen.—These fibers are contained in the plexus gastrolienalis which closely invests the artery of the same name. By determining the blood flow through this organ by means of the stromuhr, it has been shown by Burton-Opitz⁴ that the stimulation of this plexus is followed by a constriction of the splenic blood-vessels. The same result is obtained by stimulation of either splanchnic nerve. Schäffer,⁵ who has made use of a splenic oncometer, states that this preganglionic path includes vasodilators for this organ.

The Vasomotors of the Pancreas.—These fibers arise in the celiac ganglion and attain the aforesaid organ by way of the plexus hepaticus and the plexus gastroduodenalis. It seems, however, that the caput pancreatis is also innervated by fibers from the mesenteric plexus, and that the cauda pancreatis receives fibers from the neighboring splenic plexus. As far as the blood-vessels in the central mass of this organ are concerned, it has been shown by Burton-Opitz⁶ that they are innervated by fibers which ascend from the celiac ganglion by way of the hepatic plexus and the plexus gastroduodenalis.

The Vasomotors of the Liver.—This organ derives its blood supply from two sources, namely, from the hepatic artery, a branch of the

¹ Archiv de Physiol., 1896, 493.

² Pflüger's Archiv, cxxxv, 1908, 205.

³ Burton-Opitz, Am. Jour. of Physiol., cxlvi, 1914, 344.

⁴ Pflüger's Archiv, cxxix, 1908, 189.

⁵ Jour. of Physiol., xx, 1896.

⁶ Pflüger's Archiv, cxlvi, 1908, 344.

celiac axis, and from the portal vein. The former blood-vessel conveys its contents to the framework of this organ and the latter to the secretory cells. It is a well-known fact that the arterial terminals eventually unite with the intralobular radicles of the portal vein, so that both types of blood eventually attain the common collecting tube, the vena hepatica. For this reason, it must be evident that the secretory cells of the different acini cannot be rendered absolutely bloodless by the ligation of the portal vein, because a certain amount of blood will still be furnished them in an indirect way by the hepatic artery. In agreement with the histological evidence, Burton-Opitz¹ has found that the influx through the hepatic artery is always increased if the portal blood is prevented from reaching the liver by diverting it directly into the inferior vena cava through a fistulous communication (Eck fistula).

The manometric determinations of Burton-Opitz² have shown that the pressure in the hepatic artery of the dog is from 4 to 6 mm. Hg lower than that prevailing in the abdominal aorta, and from 5 to 6 mm. Hg higher than that existing in the arteria gastroduodenalis. The latter blood-vessel, as has been stated previously, forms the continuation of the hepatic artery. Upon the basis of numerous quantitative determinations of the blood flow in the hepatic artery, it has been found by this investigator that the speed of flow is 300-350 mm. in a second. This value is in close agreement with similar calculations of the velocity of the blood flow in other systemic arteries. The portal blood stream, on the other hand, progresses with a speed of only 60 to 80 mm. per second.

In the course of the experiments just cited it has been found that the pressure in the different tributaries of the portal vein amounts to about 10-14 mm. Hg and at the hilus of the liver to 8-9 mm. Hg. The latter value, therefore, indicates the pressure under which the cells of the liver acini secrete the bile which is then transferred into the biliary spaces and capillaries in which the resistance is practically zero. Moreover, as the pressure in the inferior vena cava in the vicinity of the hepatic vein is close to zero, it will be seen that the resistance which the portal blood must overcome in its passage through the liver, is very slight in comparison with the resistance offered to the blood of the hepatic artery. Clearly, as the latter arrives at this organ under a pressure only slightly below that prevailing in the abdominal aorta and leaves it under the general venous pressure, the loss is considerable. It must amount to almost 100 mm. Hg.

Quantitative measurements of the arterial influx into the liver, in a dog weighing about 15 kg., have given a value close to 3 c.c. in a second. Moreover, as the portal influx in the same period of time amounts to about 5 c.c., the total blood supply of this organ may be estimated in round numbers at about 7 c.c. per second. If this value

¹ Quart. Jour. of Exp. Physiol., iv, 1911, 93.

² Ibid., iii, 1910, 297.

is compared with the total quantity of blood present in an animal of this kind, it will be seen that the blood completes the circuit through the hepatic blood-vessels once in every three minutes. But, while the liver receives a larger supply of blood than any other structure in the body, its vascularity per unit of substance is not so great as that of the brain or kidney, because its weight is very much greater than that of the organs just named.

In agreement with its double blood supply, the liver is equipped with a vasomotor mechanism which is capable of influencing the arterial as well as the venous influx. By stimulation of the hepatic plexus, as well as of single nerves thereof, it has been proved by Burton-Opitz¹ that these intrahepatic mechanisms are innervated by the celiac ganglion. It has also been established that the aforesaid plexus conducts afferent impulses from the liver, pancreas, and duodenum to the solar division of the sympathetic system, whence they are transferred to the vagi and greater splanchnic nerves.

D. THE CEREBRAL CIRCULATION

The brain derives its blood from the internal carotid and vertebral arteries, the anastomosis of the branches of these two systems at the base of this organ being known as the circle of Willis. This reservoir serves to equalize the flow of blood to the various regions of the brain, so that the obstruction of one or more of its tributary channels cannot cause a complete anemia of this organ. Thus, if one carotid or one vertebral is obliterated, an adequate supply of blood is nevertheless obtained through the channels still left open. In fact, it has been found that one vertebral is sufficient to furnish enough blood to retain the brain in a functional condition. But, while the anastomosis is complete between the blood-vessels situated at the base of this organ, the distal or cortical vessels do not communicate very freely with one another; indeed, several of them are terminal in their character.

The cerebral veins, are classified in the same way, namely as central or ganglionic and as distal or cortical. They do not, however, descend in the path of the ascending arteries, but pursue in most cases an independent course; in fact, some of them even ascend with the arteries. Besides, the blood stream in the smaller veins is frequently opposite in direction to that in the larger collecting channel, so that a certain impediment of the flow is produced at their points of confluency. That this condition is physiological is evinced by the fact that the lumen of the chief sinus is frequently rendered uneven by trabeculæ and that the orifices of its tributaries are guarded by valves. Some sections of these collecting tubes may actually be placed in an ascending position by moving the head.

The venous sinuses of the cranial cavity of which there are eighteen, are tubular blood spaces lined with endothelium and situated between

¹Quart. Jour. of Exp. Physiol., xi, 1913, 57.

the periosteal and meningeal layers of the dura mater. In many places their channel is hollowed out in the bone, their patency being assured in addition by numerous delicate threads of dura mater fastened to their external surface. In accordance with their location, these sinuses collect the blood not only from the cortical and ganglionic veins of the cerebrum, but also from the enveloping membranes and the bones. Moreover, those situated at the base receive at least a part of the blood of the orbital cavities and the eyeballs.

Intracranial Pressure.—As has been stated above, the cranial cavity forms a natural plethysmograph for the brain. If a cannula is inserted in a trephine opening and is connected with a recording tambour, two types of oscillations will be registered, the smaller ones being caused by the action of the heart and the larger ones by the respiratory movements. They may be rendered more conspicuous by incising the dura, because this membrane places a certain resistance in the path of the expanding brain. In infants, these pulsations may be observed in the region of the fontanelles, and in adult persons through accidental defects in the skull.¹ The question, whether the cerebral blood-vessels are also expanded when the skull plates are intact, has been answered positively by Donders² and Schultze³ who have observed the brain through a piece of glass firmly fixed and sealed in a trephine opening. It seems that an interchange of pressure is still possible in spite of the fact that the brain is situated, so to speak, in a compartment possessing perfectly rigid walls. Under normal conditions, the place of least resistance is the occipitoatlantal membrane, but a slight interchange of pressure may also be effected through the carotid foramina and the points of exit of the cranial nerves.

At all events, it must be evident that the brain cannot undergo more than a very limited alteration in its volume. In the dog, for example, an expansion of only 2 to 3 c.c. is possible. A greater increase is invariably associated with a rise in the intracranial pressure and a compression of the cerebral veins. The interchange of pressure, made necessary by such slight volumetric variations as are produced by the systolic movements of the heart, is easily effected by an encroachment upon the venous blood current. Thus, we actually find that the distal venous channels pulsate synchronously with the arteries. Greater expansions of the brain are made possible by a displacement of the cerebrospinal fluid. A certain yielding is also had at the foramina intervertebralia, where the loose tissue is pressed outward whenever the cerebral fluid is subjected to an undue pressure. The tissue may also be made to give way slightly at the other cranial orifices. In the second place, we may obtain an actual transfer of the cerebral fluid into the lymph spaces of the cord or into the lymphatic channels of the neck, orbital cavity, internal ear, and cranial nerves. Further-

¹ For historical data see Hill, *The Cerebral Circulation*, London, 1896.

² *Onderzoekingen ged. in het phys. Lab. d. Utrechtsche Hoogeschool*, 1850.

³ *Med. Zeitschr., St. Petersburg*, 1866.

more, the connection between the lymphatic spaces of the cerebrum and the veins is sufficiently free to allow an escape of this liquid whenever the intracranial pressure suffers a more marked and lasting increase.

Under normal conditions, the pressure of the cerebral fluid preserves a direct relationship to the pressure of the brain, but only within certain limits. Thus, while a certain compensation is possible, its range is limited. For this reason, a decided increase in the intracranial pressure must invariably be followed by a rise in the venous pressure in consequence of the compression of the veins. This change in turn leads to a rise in the arterial pressure, because the influx of the arterial blood is thereby retarded. In the same way, a marked increase in the venous pressure, or in the general cerebral blood pressure, must be followed by an elevation of the intracranial pressure, because the spaces containing the cerebral fluid, are thereby compressed while the escape of the latter into the veins is made impossible. Conditions of this kind may be produced without much difficulty by various experimental procedures. They are also associated with different pathological processes such as tumors, extravasations of blood, an excessive production of cerebrospinal liquid, and others. In all these cases the intracranial pressure is raised beyond the limits of compensation so that a compression of the brain results which in turn is followed by far reaching and grave functional disturbances. Hindrances to the venous return, or a greater inrush of arterial blood, produce the same general effects, the only difference between them being that, in the latter instance, the cerebral blood pressure is affected first and the intracranial pressure last.

The intracranial pressure may be increased by inserting a trephine cannula in the region of the parietal lobe which is connected with a reservoir containing warmed saline solution. The dura should be incised, because this membrane is so tense that it protects the meninges against any pressure which may be produced by raising this reservoir. It will be found that the general blood pressure rises very abruptly as soon as the intracranial pressure has exceeded that of the blood. It does not remain at this high level, however, because the heart soon displays a decided diastolic tendency and ceases to beat altogether if the compression is continued for too long a time. These changes are associated with an inhibition of respiration. Two explanations have been offered for this phenomenon. Adamkiewicz has stated that it is occasioned by the mechanical damming back of the arterial blood in front of the cranial orifices, while Cushing¹ believes that it arises in consequence of a reflex vasomotor reaction. By measuring the blood flow through the carotid artery with the help of a stromuhr, Burton-Opitz and Edwards² have shown that the brain

¹ Am. Jour. of Med. Sciences, 1902 and 1903; also see: Eyster, Burrows and Essick, Jour. Exp. Med., xi, 1909, 489.

² Wiener klin. Wochenschr., 1916.

actually receives more blood during this period of heightened arterial blood pressure, and hence, it must be concluded that this reaction is of nervous origin. It seems that the increased intracranial pressure influences the cerebral centers directly and gives rise to a general reflex vasoconstriction which becomes associated later on with an inhibition of the cardiac and respiratory activities. It might be mentioned that the procedure just described may be used to imitate the chain of symptoms generally associated with certain lesions of the brain and fractures of the skull.

The Regulation of the Cerebral Blood Supply.—It has always been held that the vascularity of the brain is determined exclusively by indirect factors, such as vasomotor reactions in other parts of the body and gravity. At the present time, however, when the existence of vasomotor nerves to the cerebral blood-vessels can no longer be doubted, this purely mechanical conception must be modified somewhat to conform to actual conditions. Quite naturally, the extracranial factors just mentioned cannot be disregarded entirely, because it seems certain that they are capable at times of exerting an influence which is not inferior to that of the intracranial vasomotors. Thus, it may be stated that the vascularity of the cerebrum and neighboring structures is controlled in a direct and an indirect way, first by the vasomotor changes inside the cranial cavity and secondly, by vasomotor and other changes in more remote parts of the body.

This conclusion, however, need not defer us from briefly discussing the older view of Roy and Sherrington, which contends that the vascularity of the brain is controlled solely in an indirect way by vasomotor reactions occurring in other parts of the body. The claim is made that two circuits are chiefly concerned in this interchange, namely, the portal and the cutaneous. It is readily conceivable that a dilatation occurring in one or both of these vascular areas must lead to a withdrawal of a certain quantity of blood from the cerebral blood-vessels. Contrariwise, it may be inferred that a constriction in either region must force a certain quantity of blood into the cerebral circuits. In substantiation of this view, Mosso¹ has shown that a constriction of the blood-vessels of the legs is always associated with an increase in the volume of the brain. These observations were made upon men with trephine openings in the skull, their limbs having been enclosed in a plethysmograph. Quite similarly, it has been observed by this author that the volume of the brain is diminished during sleep, while that of the limbs is increased. A constriction of the blood-vessels of the posterior extremities takes place whenever the mental activity is heightened and especially during emotional states. We have seen above that the portal organs require an increased amount of blood during digestion and that this extra supply of blood can only be obtained by withdrawing it from other parts of the body, inclusive of the cerebrum. Concurrently, it may be gathered that the cerebrum

¹ Mosso, Ueber den Kreislauf des Blutes im mensch. Gehirn, Leipzig, 1881.

necessitates the transfer of a certain quantity of blood from the portal organs and the cutaneous tissues, whenever it is called upon to do extra work. At all events, it is certain that these systems bear a reciprocal relation to one another, so that, for example, the processes of digestion and mental activity should never be closely associated.

Changes in the blood supply of the brain may also be effected in an indirect way by various sensory impressions derived from the skin and subcutaneous tissues. Thus, the immersion of the body in moderately cold or warm water, or its exposure to cold or warm air, produces, on the one hand, a vasoconstriction and, on the other, a vasorelaxation. In the former case, the blood flow through the cerebrum is augmented and, in the latter, diminished. These changes are generally associated either with a greater or a lesser mental and bodily alertness. Account should also be taken of the fact that these vasomotor reactions are usually accompanied by changes in the energy of the heart and in the frequency and amplitude of the respiratory movements.

PART IV

RESPIRATION, VOICE AND SPEECH

SECTION XII

RESPIRATION

CHAPTER XXXVI

THE STRUCTURE AND FUNCTION OF THE ELEMENTARY LUNG

Introduction.—In its widest sense the term respiration is applied to the interchange of the gases between living substance and the medium in which it is contained. This is true of animals as well as of plants, and since by far the greatest number of protoplasmic entities take up oxygen and give off carbon dioxid, respiration is practically restricted to the acquisition of the former gas and the discharge of the latter. Oxygen is also taken into the body in other ways, for example, as a constituent of the food, but it is practically impossible for the cells to make use of it in this form. This implies that the cells do not possess the power of separating it from its combinations and hence, it is evident that this gas must be presented to them in an easily assimilated form, namely, as “respiratory oxygen.”

It is commonly held that animals inhale oxygen and exhale carbon dioxid, while plants inhale carbon dioxid and exhale oxygen. In this way, it is assumed, a continuous equilibrium of these gases is had for all time to come. As a matter of fact, however, plants possess the same respiratory interchange as animals, oxygen being inspired by them and carbon dioxid expired. Nevertheless, it is true that plants, when exposed to sunlight, liberate oxygen, but this excess of the gas does not find its origin in a respiratory activity but in an increased metabolism which is associated with the assimilation of the starches.

If we regard the bacteria as members of the animal kingdom, a classification which is not at all uncommon at the present time, it may be said that animals are either *aërobic* or *anaërobic*. This designation is intended to convey the idea that some of them thrive

only in a medium containing oxygen, while others, for example, the bacillus of tetanus and the bacillus of anthrax, flourish only when this gas is absent. It need scarcely be emphasized that by far the greatest number of organisms are aërobic, *i.e.*, they take in oxygen and give off carbon dioxid.

Diffusion Pressure.—In the same way as the air moves from an area of high pressure to an area of low pressure, so do the individual gases constituting a mixture, move from places of high to places of low pressure. The driving force responsible for this movement of diffusion, is furnished by the partial pressures of these gases. The atmospheric air rests upon us with a certain pressure which differs somewhat with the temperature, altitude, and other conditions. For this reason, it is necessary to have a fixed standard which is called an *atmosphere*. This pressure is capable of supporting a column of mercury 760 mm. in height at latitude 45° and at sea-level, when the temperature of the mercury is 0° C. But as air is composed of several gases, the total pressure of 760 mm. Hg is equal to the sum of the separate pressures of its constituents. Inasmuch as the pressure exerted by each gas in a mixture is known as the partial pressure of that gas, the pressure of the air is really the product of the different partial pressures of its constituents.

Dry atmospheric air shows the following composition:

Oxygen.....	20.94 per cent.
Nitrogen.....	78.40 per cent.
Argon, krypton, neon.....	0.63 per cent.
Carbon dioxid.....	0.03 per cent.

As the partial pressure exerted by a certain gas is proportional to the quantity of this gas present in the mixture, it can readily be seen that the partial pressure of the oxygen equals in round numbers $\frac{21}{100} \times$

760 = 159.6 mm. Hg, and that of the nitrogen $\frac{79}{100} \times 760 = 600.4$ mm. Hg. Carbon dioxid exerts practically no pressure at all in perfectly fresh air.

Diffusion.—In the lowest forms the interchanges of the gases is effected by simple diffusion. The medium, whether it be water or air, contains a certain normal quantity of oxygen. It is held here under a definite partial pressure. Inside the organism, on the other hand, the partial pressure of this gas is much less, because it is constantly used up during the processes of oxidation. On this account, it is present here in smaller amounts than in the medium. Obviously, therefore, the molecules of oxygen must move in a steady stream from without to within directly through the enveloping membrane. The latter, quite naturally, offers a slight resistance to the diffusing particles, but the difference in the partial pressures is so great that this movement as a whole is not noticeably hindered. Quite similarly, the fact that carbon

dioxid is constantly liberated during the oxidations proves that its partial pressure is higher inside the organism than in the medium, and hence, the molecules of this gas must move outward, *i.e.*, in a direction opposite to that of the particles of oxygen. Brief mention should also be made of the fact that nitrogen is a functionally inert gas, serving merely as the medium in which the diffusion of the other two gases takes place. The function of argon, krypton and neon is not understood as yet, but it seems that they are of no importance in respiration.

With the gradually increasing size and complexity of the organisms this method of interchanging the gases becomes wholly insufficient, because the diffusion-pressures are not high enough to drive the oxygen directly into the innermost recesses of a multicellular body. Invaginations make their appearance which finally take the form of small pouches suspended in the body cavity and communicating with the outside through small openings. This is the beginning of the lung, a specialized organ set aside for the purpose of bringing the air into close relation even with those cellular units of the body which under ordinary conditions could not be reached by direct diffusion. This end is then attained in an indirect manner with the help of the body fluids. To begin with, an interchange of the gases takes place in the lungs, where the atmospheric air is brought into relation with the blood. This process is known as *external respiration*. The freshly aerated blood is then directed to the different parts of the body, where it enters into a vivid interchange with the tissues through the intervention of the lymph. This process is designated as *internal respiration*. In all the higher animals, therefore, two centers for the diffusion of the gases are in existence, namely, one in the lungs and one in the tissues.

The Elementary Lung.—In its most elementary form the lung consists of a pouch-like invagination of the body-surface, containing air from which oxygen is constantly abstracted, while carbon dioxid is passed into it. But if this air were perfectly stationary, an equalization of the partial pressures would soon result, which in turn would lead to a cessation of the diffusion. Obviously, therefore, it is imperative that the original partial pressures be maintained and this end can only be accomplished by frequently renewing the air in this pouch. If this is done at regular intervals, as the metabolism of the body may demand, the diffusion will continue at its normal height during the entire life of the animal.

The question may now be asked, how is this renewal of the air effected? Inasmuch as the lung is connected with the outside by means of a relatively long and narrow tube, its contents are well protected against all movements of the atmospheric air. Consequently, the intake as well as the outgo of the air must be accomplished by a definite activity on the part of the body, in which, however, the lung plays only a passive part. The lung as such does not possess the power of increasing or decreasing its size, and hence, is quite unable to pro-

duce an inflow and outflow of air. Instead, it is to be clearly understood that the size and capacity of this organ are varied by an outside force which is applied to its entire external surface. This force is dependent upon the activity of certain muscles, classified as respiratory muscles, the sole function of which is to produce an enlargement of the thorax and, in an indirect way, also of the lung. Consequently, the expansion of this organ is a passive phenomenon as far as the lung is concerned, but active as far as the muscles are concerned. This phase is soon followed by a decrease in the size of this particular part of the body and a decrease in the size of the lung. The former period is known as *inspiration* and the latter as *expiration*.

The principle involved in this process is well illustrated by the behavior of the air-sacs of the insects. In these animals we find a branched system of tubes which communicate through narrow orifices,

FIG. 227.—DIAGRAM OF AN ELEMENTARY LUNG.

S, stigma; O, oxygen diffusing from air of sacculle into tissue fluids; CO_2 , diffusing in reverse direction.

known as *stigmæ*, with small saccules suspended in the body cavity. On observing an insect it will be seen that the volume of its trunk is rapidly changed from moment to moment. The walls of its body are moved outward by muscular force, the air-sacs are expanded and air rushes through the *stigmæ* into their interior. At this time, therefore, the pressure within is lower than without. Toward the end of inspiration an equilibrium is slowly established which causes a cessation of the influx of air. The

expiratory movement now sets in. The body wall moves into its former position largely by recoil with the result that the air in the saccular spaces is subjected to a pressure higher than that of the atmosphere. The air now escapes through the *stigmæ* until an equalization of the pressures has again been attained. This alternate expansion and compression of these air-spaces enables them to obtain a constant supply of fresh air by means of which the partial pressures and the diffusion of the gases may be kept up indefinitely.

Special Respiratory Organs.—Animals may be divided into two classes, namely, into those living in atmospheric air and those living in water. Accordingly, two types of respiratory organs have been developed, namely, the lungs and the gills, the latter being the phylogenetically older mechanism. Moreover, those animals which spend their life in part in the former medium and in part in the latter, are in possession of lungs as well as gills. It is true, however, that these organs are generally not functional at the same time, because the change of an aquatic into a terrestrial animal is usually associated with a gradual atrophy of the gills.

In principle the *structure of the gills* is the same as that of the lungs. In both cases the blood is brought into almost direct contact with the medium, remaining separated from it only by a layer of flat endothelial cells. Hence, the gills may be likened to a lung, which, so to

FIG. 228.—DIAGRAM ILLUSTRATING THE FUNCTION OF THE GILLS.

W, the water is driven across the surfaces of the gill-plates, whence *O* diffuses into the gill capillaries and *CO₂* out of them.

speak, has been turned inside out (Fig. 228). Naturally, the size of the respiratory surface of this organ differs greatly in accordance with the metabolism of the different animals. The individual plates become more numerous and frequently extend as fringed folds far out

FIG. 229.—DIAGRAM ILLUSTRATING THE FLOW OF THE WATER THROUGH THE MOUTH CAVITY OF A BONY FISH. (After Dahlgren.)

A, inspiration; B, expiration; M, cavity of the mouth; D, esophagus; G, gills; MV, maxillary valve; BV, bronchostegal valve; OP, operculum moves outward on inspiration, opening MV and closing BV. On expiration operculum moves inward, closing first valve and opening second valve.

into the water. These gill-plates are supplied with venous blood which after its oxygenation is returned into the dorsal aorta.

In illustration of the method by means of which the individual plates are constantly supplied with fresh water, we might briefly consider the respiratory mechanism in the teleosts (Fig. 229). An

expansion of the oral cavity *M* is effected during inspiration by the raising of the opercular apparatus, *OP*. The branchiostegal membrane *BV* moves inward at this time closing the gill passages, while the membranous fold which projects downward from the roof of the mouth in the maxillary region and meets a similar partition from the floor of the mouth in the area of the mandible, moves inward and permits the water to enter this cavity, *MV*. During the succeeding expiration the contraction of the opercular apparatus increases the intraoral pressure and in turn closes the aforesaid mandibulomaxillary valve, but opens the branchiostegal valve. Obviously, therefore, the cavity of the mouth plays the part of a force pump, the flow of the water through it being determined by the position of these valves.

The *swim-bladder* or *air-bladder* of the fishes possesses the same origin as the lungs. It arises from an outgrowth of the forepart of the alimentary tract, but becomes specialized in most of these animals to serve merely as a hydrostatic organ. Its duct, known as the ductus pneumaticus, is entirely obliterated, and hence, it is evident that the gas contained in it must pass directly through the cells lining its wall. Simple diffusion fully explains this process, but it must also be taken into account that its wall contains sometimes small tubular glands which appear to be there for the purpose of actively secreting a gas, presumably oxygen. In some fishes, however, the duct remains open so that the swim-bladder may also act as an accessory respiratory organ.

In some animals, the *interchange of the gases is effected with the help of the intestinal canal*. A certain quantity of air is swallowed which later on escapes through the anus much poorer in oxygen (12 per cent.) but richer in carbon dioxide (0.8 per cent.). In warm-blooded animals, intestinal respiration plays only a very insignificant rôle. The oxygen swallowed with the food is absorbed, but only very slight amounts of carbon dioxide diffuse into the intestinal contents. Quite similarly, hydrogen and other gases which are formed in the course of digestion may pass into the blood to be subsequently discharged in the expiratory air.

Of much greater general importance is the *respiratory interchange through the skin*. In the lower types of worms and arthropods, the deeper layer of the integument embraces numerous networks of capillaries which play the part of gills as the sole means by which these animals are enabled to effect a proper interchange of the gases. Amphibia are also much dependent upon the skin as an accessory organ of respiration. In man the integument is rather impermeable, but Schierbeck¹ states that the carbon dioxide discharged in this way may amount to 9 grams in 24 hours or to less than 1.0 per cent. of the total output. This quantity may be considerably increased by sweating or by raising the temperature of the surrounding air. The oxygen

¹ Archiv für Anat. und Physiol., 1893, 116.

intake through the skin is much less than the discharge of carbon dioxid.

In this connection mention should also be made of the fact that the *lungs of birds* are beset with many appendages, or air-sacs, which communicate with the bronchi by special tubules and frequently extend into the bones, or for some distance between the muscles and underneath the skin. These air-sacs must be regarded as integral parts of the respiratory apparatus, although they tend to render the entire body more buoyant. The metabolism of birds is very intense and subject to considerable fluctuations. Thus, this additional respiratory surface may be called upon at any time to effect a more intense and rapid interchange of the gases without necessitating an undue expansion of the lung tissue itself.

The interchange of the gases in the placenta of the mammals is responsible for the difference in the character of the blood of the umbilical artery and vein. As the blood of the latter vessel contains more oxygen and less carbon dioxid than that of the former, it must be evident that this organ is the seat of diffusion processes between the body fluids of the embryo and mother.

The Complex Lung.—To begin with, the lung consists of a single sac which possesses no dividing septa and extends in many cases through the entire length of the body cavity. In the amphibians the organ becomes paired, consisting of two elliptical pouches of about equal length which communicate with the pharyngeal cavity through the bronchi and the trachea (Fig. 230). Furthermore, the breathing surface of these sacs is increased enormously by membranous partitions which project far into the lumen of the main cavity. Thus, a beginning is made of a differentiation of the lung into numerous smaller compartments which are commonly designated as air-cells or alveoli. While some of the reptiles retain this type of lung, many of them show a much higher state of development of this organ, because the individual alveoli are entirely separated from the main cavity and communicate with the latter only through small orifices. In these we recognize the beginnings of the bronchiolar tubules. With the increasing alveolization of the lung, the bronchi and bronchioles are really separated into an "extra pulmonary" system of tubes which are generally provided with solid cartilaginous rings and eventually also with muscular tissue. The capillary networks which at first are restricted to the very

FIG. 230.—DIAGRAM ILLUSTRATING THE FUNCTION OF THE AMPHIBIAN LUNG.

T, trachea; B, bronchi; L, lung of one side; P, septa dividing the main cavity into smaller air-spaces or alveoli (A).

walls of the lungs, eventually invade the membranous partitions. As a result of this extension, a much larger sheet of blood is brought into direct diffusion contact with the air in the alveoli.

The mechanism of respiration in these animals is very simple. The floor of the mouth is depressed by muscular activity so that the pressure within this cavity falls below that of the outside air. A certain quantity of air then enters through the nostrils until an equalization of pressure has been effected. The nostrils are then closed and the glottis opened. The subsequent elevation of the floor of the mouth now forces the air into the lungs. Here it remains for a time until a part of it is allowed to escape through the opened glottis and nostrils

FIG. 231.—HUMAN RESPIRATORY APPARATUS SHOWING THE BRANCHING OF THE BRONCHI IN THE INTERIOR OF THE LUNGS. (Dunal.)

in consequence of the passive recoil of the parts previously put under elastic tension. This mechanism again illustrates the action of a force-pump.

The Mammalian Lung.—The lung of the mammal exhibits several of the characteristics of the reptilian lung. Beginning at the pharyngeal cavity, the *trachea* with its modified upper portion, known as the larynx, passes backward for a distance of about 12 cm. and divides into two main branches, the *bronchi*. The latter subdivide again and again until small terminals, or *bronchioles*, are obtained which individually connect with irregular spaces, known as *infundibula*. These in turn are made up of a number of minute cellular spaces, or *alveoli*.

The smaller bronchioles are not in possession of a cartilaginous framework, but consist merely of fibrous and elastic tissue and a scanty layer of smooth muscle cells. The larger tubes, on the other hand, are equipped with rings of cartilage to render them more resistant against the variations in pressure to which they are subjected during each respiratory act. This entire tract is lined with a layer of epithelium which, in the trachea, bronchi and bronchioles, is of the ciliated columnar variety and, in the outer parts of the infundibulum, cuboidal in shape. The effective stroke of the cilia is in the direction of the mouth, so that much of the foreign material carried in with the air is again expelled without extra efforts. The specialized respiratory epithelium is restricted to the alveolar walls. These are composed of connective tissue containing a large number of elastic fibers and an external lining of very flat and large cells. The elastic tissue, as we shall see later, is responsible for the traction which the lung constantly exerts upon the internal surface of the chest wall.

FIG. 232.—DIAGRAM ILLUSTRATING THE ARRANGEMENT OF THE INFUNDIBULA.

B, Bronchiole; *D*, infundibular duct; *J*, infundibulum; *A*, alveolus; *S*, interinfundibular space, occupied by capillaries.

The blood-vessels ramify in all directions through the interalveolar walls; moreover, as the infundibular vesicles are packed close together, the blood is brought into intimate relation with the air, being separated from it merely by the lining cells of the capillaries and alveoli. In fact, in some of the higher animals (birds) the alveolar walls seem to be devoid of lining cells. It should also be remembered that by far the largest quantity of blood furnished by the pulmonary artery, serves respiratory purposes only. Thus, if a man weighing 70 kilos, possesses 4.5 kilos of blood, not less than 700 grams of this amount are contained in the pulmonary blood-vessels. Furthermore, if the circulation-time in the lesser circuit is reckoned at 13 seconds, it will readily be seen that close to 200 kilos of blood traverse the lungs in an hour and 4500 kilos in a day. A very small portion of this blood is required for the nutrition of this organ, but it seems that this amount is derived directly from the aorta by those arterial branches which are distributed to the bronchi, interlobular septa, pleural membranes and the trunks of the blood-vessels leaving the heart. The venous return from these parts

is effected by the corresponding veins, but some of this blood also finds its way into the pulmonary veins by anastomoses.

The diameter of the alveoli varies between 120 and 380 μ , their average diameter being 120 μ . Inasmuch as from 300 to 400 millions of alveoli are contained in each lung, and inasmuch as one of them possesses an area of about 0.321 mm.², the total respiratory surface must amount to 130 m.² in men and to 104 m.² in women. If these values are now compared with the size of the body-surface, it will be seen that the latter is 100 to 125 times smaller than the respiratory surface of our lungs. It must be evident, however, that the area formed by the pulmonary blood is somewhat smaller than the alveolar surface, because the capillaries do not occupy the entire extent of the alveolar surface. Thus, it has been estimated that, if all the blood present in the lungs of a man, could be made to form a single layer measuring 10 μ in thickness, it would cover an area of 120 m.². These figures, very naturally, are only approximately correct and are not intended to be memorized but simply to permit us to form an idea regarding the enormous surface of blood brought into relation with the outside air.

CHAPTER XXXVII

THE MECHANICS OF THE RESPIRATORY MOVEMENTS

General Topography.—The lungs of the mammal are contained in the cavity of the thorax which forms the fore part of the general

FIG. 233.—ILLUSTRATION TO SHOW THE POSITION OF THE LUNGS IN THEIR RELATION TO THE WALL OF THE THORAX.

cavity of the trunk. They are surrounded on all sides by relatively solid walls, made so by a copious inlay of bony laminæ. From the abdominal cavity they are completely separated by a muscular septum, the diaphragm, but communicate with the pharyngeal, nasal

and oral cavities by a relatively narrow tube, known as the trachea. This almost air-tight compartment of the thorax possesses a conical outline, its tip being situated at the root of the neck and its base at the diaphragm. Its ventral wall is formed by the sternum and adjoining costal cartilages, its sides by the ribs, and its dorsal wall by the vertebral column.

The two lungs occupy almost the entire thoracic cavity, only its central extent being allotted to the heart and large blood-vessels with their pericardial investment. Each organ is closely enveloped by a delicate membrane which is reflected from the bronchi and lines the entire internal surface of the chest wall. Consequently, this membrane which is known as the *pleura*, consists of two layers, an outer or *parietal* and an inner or *visceral*. The opposing surfaces of these layers are lined with flattened endothelial cells and are moistened with a lymphatic secretion to prevent frictioning. It must be emphasized, however, that the layers of the pleura always remain in close contact with one another and that an actual pleural cavity cannot be present so long as the walls of the chest remain intact. Under normal conditions, therefore, the visceral and parietal layers of the pleura act as one membrane which is interposed between the chest wall and the substance of the lung to facilitate the movement coincident with the expansion of this organ. Between the left and right pleural sacs is a space, known as the mediastinum, which is divided into an anterior and a posterior compartment by the heart with its pericardial investment. In some animals, such as the rabbit, this interpleural space is broad, so that it is possible to expose the heart through the median line of the sternum without rupturing the pleural sacs. But a procedure of this kind is not feasible in most mammals, because the anterior borders of the lungs extend almost to the median line of the thorax.

THE RESPIRATORY CYCLE

The muscular act by means of which the air in the pulmonary passages is constantly kept in a fresh state, consists in an alternate increase and decrease in the size and capacity of the thorax which in turn results in a corresponding alteration in the size of the lungs. In spite of their relative solidity, the walls of the chest are flexible so that they may be moved either away from or toward a common center. The former movement takes place during inspiration and the latter during expiration, and naturally, as the intrapulmonary passage stands in communication with the outside through the trachea, an inflow of atmospheric air must result during the expansion of the lung and an outflow during its subsequent period of recoil. Concurrently, it may rightly be inferred that the outward movement of the chest wall may be greatly restricted by obstructing the trachea, because this would prevent the inflow of air and hence, nullify the volumetric increase in the capacity of the chest which in turn gives rise to the expansion of the lungs.

The chest is never at rest but is either in the position of inspiration or expiration, and hence, the respiratory cycle is one of constant activity. Between the end of every expiration and the beginning of the succeeding inspiration the thorax exhibits a condition of quiescence which is sometimes erroneously designated as the respiratory pause. Thus, it may be stated that the respiratory cycle includes a dynamic and a static phase, the former consisting of the inspiratory and expiratory periods, and the latter of this period of comparative passiveness and rest. It should be remembered, however, that the elasticity of the lungs and of the parts forming the thoracic walls does not cease to act even during the respiratory interims, when the muscle tissue is actually in a state of rest. For this reason, it may justly be said that a true pause does not exist during life, although it may be produced experimentally. Hence, the term static should be used solely in a relative sense.

FIG. 234.—DIAGRAM ILLUSTRATING THE COURSE OF THE PLEURA.

T, trachea; *L*, lung; *H*, heart; *A*, abdominal cavity; *C*, collapsed lung (the rest of this cavity being filled with air (pneumothorax); *V*, visceral pleura; *P*, parietal pleura reflected from root of lung (dotted line).

A. THE STATIC PHASE.

At the end of expiration the thorax and the organs contained therein maintain for a very brief time a position from which several of the fundamental principles of respiration may readily be inferred. The entire cavity, with the exception of the mediastinal space, is filled by the lungs which are everywhere in immediate contact with the internal surface of the chest wall. Externally, they are protected against the atmospheric pressure by the relatively solid framework of the thorax and atmospheric pressure prevails in all the intrapulmonary spaces and passages.

Collapse of the Lung.—A very different picture is presented if the air is permitted to act upon the outside surface of the lung. This end can be attained by puncturing the pleural cavity in any intercostal space or by forming a communication between this cavity and the respiratory passage. The former condition frequently results in consequence of gunshot or stab wounds, and the latter, in consequence of perforations through tuberculous lung tissue. The opening of the pleural cavity is immediately followed by the retraction of the external surface of the corresponding lung from the internal surface of the chest wall, the intervening space being filled with air. This condition which is known as *pneumothorax*, cannot be remedied as long as the opening in the pleural cavity remains patent; in fact, the air entrapped in the collapsed organ is then gradually absorbed, while the formerly buoyant tissue solidifies and loses its function permanently. Obviously, a lung which has lost its elasticity does not collapse readily, but tends to preserve its original volume (emphysema).

If the communication between the pleural space and the outside is again closed, the air in this cavity is slowly absorbed with the result that the lung gradually increases in volume until it again lies everywhere in contact with the chest wall and can again be subjected to normal degrees of expansion. It might also be mentioned that the collapse of one lung need not necessarily prove fatal, because the opposite organ is capable of a certain degree of hyperexpansion which will tend to make up for the loss sustained on the opposite side. In addition, it is noted that the normal organ most generally acquires a certain amount of new tissue which will enable it in time to perform its compensatory function in a more complete manner. Attention might also be called to the fact that perforating wounds of the lung are not always followed by a collapse of the injured organ, because the weapon may again be withdrawn without that the air has had a chance to enter the intrapleural space. The diameter of the modern bullet is so small and its velocity so great that the parts are scarcely lacerated and are still able to recoil and to close the defect almost immediately.

Another condition in which similar conditions prevail is pleurisy. The dry stage of this inflammatory reaction having been passed, a serous exudate forms upon the pleural surfaces which in time gravitates into the most dependent portion of the intrapleural space and gradually separates the visceral from the parietal pleura. Eventually the lung is pushed far away from the wall of the thorax until its volume scarcely exceeds that of a collapsed organ. Conditions of this kind constitute *hydrothorax*. During the subsequent period of absorption, this exudate is gradually removed with the result that the lung is slowly drawn toward the chest wall until the pleural cavity is again converted into a potential capillary space. In this connection mention might also be made of the fact that the compression and resultant reduction in the respiratory capacity of this lung may be relieved by withdrawing the fluid with the help of an aspirating syringe.

Intrapleural, Intrathoracic and Intrapulmonic Pressures.—The foregoing conditions have been discussed somewhat at length, because

they illustrate in a most convincing manner the principle upon which the mechanics of respiration are based. They prove first of all that the lungs are held in firm contact with the internal surface of the chest wall by a definite force, the removal of which immediately allows the pulmonary tissue to separate itself from the wall of the thorax. In the second place, they prove in an unmistakable manner that the tissue of the lung is elastic, and that it is constantly held in a state of hyperdistention. On this account the wall of the chest is always exposed to the elastic recoil of the lungs, the tendency of which is to allow the stretched interalveolar fibers to regain their normal length and shape. Obviously, therefore, these organs are always kept in an expanded state by a force resting upon their external surface and not by a force acting upon the walls of the respiratory passage from within. In other words, the lungs are not inflated by a current of air forced in through the trachea, but are expanded from without, this movement causing air to flow into their recesses. Consequently, excepting the elastic recoil during expiration, the lungs do not actually participate in an active way in the shifting of the respiratory air.

The force which keeps the lungs in contact with the internal surface of the chest wall is the pressure prevailing in the intrapleural space. In the nature of things, it is the pressure which the elastic power of the lungs would have to overcome in order to pull the pleural layers apart, but as the capillary space between the latter is closed, the recoil of the pulmonary tissue is much too slight to overcome this resistance. It follows, therefore, that the lungs and the chest wall must remain in the closest possible opposition. Supposing, moreover, that the pressure in the passages of the lung amounts to one atmosphere, or 760 mm. Hg, the pressure to which the heart, great vessels, and other structures of the thoracic cavity are exposed, must be less than this figure, because the elastic tension of the pulmonary tissue constantly opposes and counterbalances the atmospheric pressure. Thus, it must be clear that the pressure prevailing immediately outside the surfaces of the lungs, *i.e.*, in the intrapleural space, must be that of the atmosphere minus the elastic recoil of the lung tissue.

In attempting to measure this elastic pull of the pulmonary tissue Donders¹ connected the trachea of a dead animal with a mercurial manometer and permitted the lungs to collapse by perforating the chest wall. Quite naturally, the recoiling lungs placed the air within them under a certain pressure, a fact which was most clearly betrayed by the outward movement of the column of mercury. It was found in this way that the lungs are capable of counterbalancing a mercurial column about 6 mm. in height and hence, if this figure is subtracted from 760 mm., the resulting value of 754 mm. indicates the pressure prevailing in the intrapleural space and other regions of the thoracic cavity outside the respiratory channel.

¹ Zeitschr. für rat. Med., iii, 287.

Practically the same result has been obtained by connecting a manometer with the intrapleural space by means of a hollow tube which is inserted through an intercostal space (Fig. 235). On piercing the parietal pleura, the visceral layer is pushed ahead of the probe (*P*) so that its free end comes to lie in a recess of the intrapleural cavity, and is directly exposed to the elastic recoil of the lung. In this particular case, the mercury in the manometer (*M*) is drawn toward the chest causing its proximal limb to rise and its distal limb to fall until the negativity in the thorax has been counterbalanced exactly. The manometer therefore, measures, the traction which is brought to bear upon the internal surface of the chest wall by the recoiling pulmonary tissue and the force with which it opposes the pressure in the respiratory

FIG. 235.—DIAGRAM ILLUSTRATING THE MANNER OF INSERTION OF A CANNULA INTO THE INTRAPLEURAL SPACE.

T, trachea; *L*, lungs; *H*, heart; *A*, abd. cavity; *P*, a probe is pushed through the intercostal space forcing the lung away from the chest wall and thus creating an artificial space; *M*, the manometer then indicates the elastic pull of the lungs; *S*, stopcock to prevent ingress of air before manometer is in place; *K*, kymograph for recording the intrapleural pressure.

passage. Hutchinson¹ has attempted to measure the elastic force of freshly excised human lungs by distending them with known amounts of air. Upon these figures Heynsins² bases his conclusion that the intrapleural pressure during the static phase of the thorax amounts to -4.5 mm. Hg. For dogs and rabbits the values of -3.9 mm. and -2.5 mm. Hg respectively have been found.

It must be evident that the term intrathoracic pressure indicates the pressure prevailing elsewhere in the thoracic cavity outside the pulmonary passage. Consequently, the terms *intrapleural* and *intra-*

¹ Hermann's Handb. der Physiol., iv, 225

² Pflüger's Archiv, xxix, 1882, 265.

thoracic pressure apply to one and the same phenomenon, but while the former has reference only to the intrapleural space, the latter includes all regions of the thoracic cavity in which its contents are subjected to the elastic pull of the lungs. The term *intrapulmonic pressure* is indicative of the pressure prevailing in the air passages of the lungs. At the end of inspiration, as well as at the end of expiration, the pressure in the respiratory channels equals that of the air without. No movement of the air is possible as long as the pressures remain equal.

The Cause of the Negativity of the Intrathoracic Pressure.—During intra-uterine life the lungs are atelectatic, *i.e.*, they contain no air. The walls of their alveoli and smaller tubules are in opposition, while the larger passages contain in all probability a moderate quantity of fluid material. Their solidity leads us to infer a high specific gravity,

FIG. 236.—DIAGRAM ILLUSTRATING THE ORIGIN OF THE INTRATHORACIC PRESSURE.

A, at birth the lungs contain no air and fill the cavity of the thorax completely; B, after the first respiration the cavity of the thorax is much enlarged in size by the outward movement of the chest walls. Consequently, air is drawn into the recesses of the lung.

a fact which is employed as a basis for an important medicolegal test. Thus, the lungs of a still-born infant sink when placed in water, while an organ which has been expanded is buoyant and able to carry not only the weight of its own tissue but also that of the heart and large blood-vessels. From this we may draw the conclusion that the lungs of the fetus are under no elastic tension and fill the thoracic cavity completely. Consequently, the capacity of the latter must equal the volume of the lungs, and hence, it must be possible to puncture the chest wall without producing a collapse of these organs.

At birth, however, the violent muscular efforts immediately give rise to an outward movement of the walls of the thorax and an increase in the size of this cavity. Moreover, as the external surface of the lungs is in firm opposition with the chest wall, it is drawn outward with the result that air now rushes into its innermost passages and recesses. To begin with, only a limited number of alveoli are rendered air-containing, but the succeeding movements distend them in increasing numbers until the organ as a whole becomes fully expanded. Most

generally, several days are required before the infantile lung is distended in its entirety. But, the important fact to remember is that the rather sudden increase in the capacity of the thoracic cavity occasions an equally abrupt increase in the volume of the lungs which is made possible only by an influx of air into its passages. In this way, the walls of the different alveoli are put on the stretch and are held in this position throughout the life of the individual. At this very moment arises the elastic recoil of the pulmonary tissue, *i.e.*, the attempt of its constituents to resume their former length and shape. Upon this recoil depends the negative pressure in the thoracic cavity; and clearly, as this difference in the capacity of the thorax and the volume of the lungs is present at the end of expiration and even after death, this negativity is a permanent condition, which may be removed only by perforating the chest wall. It is true, however, that this negative pressure is very slight during the first four days of extra-uterine life, and amounts to only -0.4 mm. Hg at the end of one week. Subsequent to this time a much greater negativity is gradually developed, because the wall of the chest now becomes more resistant and grows more rapidly than the lung. In order to overcome this difference the lungs are slowly subjected to an even greater expansion, tending to accentuate their elastic tension and to increase the negativity of the intrathoracic pressure. From these facts it may also be gathered that the lungs of the infant are more thoroughly emptied with each respiratory act than those of the adult.

B. THE DYNAMIC PHASE

The Respiratory Movements.—The phenomena presented by the active lung, are in no way different from those previously considered. We must remember first of all that the lung remains in firm contact with the chest wall, because its elastic recoil is not sufficient to allow it to separate the visceral from the parietal surface of the pleura and to create a real intrapleural space. Consequently, it must be evident that its degree of expansion is wholly determined by the position of the wall of the thorax. If the latter moves outward, the external surface of the lung must follow in the same direction and give rise to an expansion of the entire organ. Air then rushes into its inner passages. During the succeeding expiratory phase, the chest wall moves inward. The lung then recoils in a certain measure and drives a definite quantity of air to the outside. Obviously, therefore, the lung plays the part of a passive tissue, the active factor being the chest wall.

The respiratory movements consist of an alternate outward and inward movement of the wall of the thorax which leads first to an increase and then to a decrease in the capacity of this cavity and a corresponding change in the distention of the lungs. The former movement, constituting *inspiration*, is the result of the activity of the muscles of inspiration, whereas the latter, constituting *expiration*, is a

passive process, depending mainly upon the elastic recoil of the parts previously put on the stretch. The enlargement of the thoracic cavity is accomplished in three directions, namely, along its vertical, transverse and anteroposterior planes.

The increase in the vertical diameter is effected with the help of the diaphragm. This musculotendinous septum which forms the dividing line between the thoracic and abdominal cavities, arises from the first three or four lumbar vertebræ and adjoining fascia, from the borders of the six lower ribs and from the ensiform cartilage. The individual fibers strive radially toward a common center, keeping first in close

FIG. 237.—APPARATUS ARRANGED FOR ILLUSTRATING THE EXPANSION OF THE LUNG.

N, bell jar; B, rubber balloon; M, manometer. The rubber membrane closing the bell jar is pulled down in imitation of the contraction of the diaphragm. This causes the expansion of the balloon by a negative pressure resting upon its surface. The upward movement of this membrane corresponds to expiration. The manometer is connected with the space between the walls of the bell jar and the balloon (intra-pleural space) and registers the changes in pressure. (*Laulanié.*)

contact with the chest wall but later on turning rather abruptly to be inserted into the edges of the tendinous central area of this septum. The latter generally conforms to the outline of the body and appears most frequently in two segments, a right and a left (Fig. 239). In cross-section, therefore, the diaphragm presents a dome-shaped outline, its convex surface being turned into the thoracic cavity. At the side, only the smallest possible space separates its upper surface from the wall of the chest so that its parietal pleura lies in absolute contact with the parietal pleura lining the inner surface of the thorax. At a somewhat higher level, this capillary space, which is known as the "complementary" pleural cavity, soon widens out into the general cavity of the thorax.

As the diaphragm contracts, its tendinous portion is pulled downward, so that this septum as a whole assumes a much flatter outline

FIG. 238.—DIAGRAMMATIC SECTIONS OF THE BODY IN A, INSPIRATION; AND B, EXPIRATION; TR, TRACHEA; ST, STERNUM; D, DIAPHRAGM; AB, ABDOMINAL WALLS. THE SHADING ROUGHLY INDICATES THE STATIONARY AIR. (From Huxley's "Lessons in Elementary Physiology," Macmillan Co., Publishers.)

(Fig. 239). Its shape now resembles that of a flat cone, because while its tendinous part is drawn downward into the abdominal cavity, its contracted muscular part pursues a rather straight course between its place of origin and its insertion. In this way, the breadth of the "complementary" pleural space is much increased, thereby allowing the tapering inferior borders of the lungs to descend into it. It should also be remembered that the downward movement of the diaphragm is greatly restricted in the region of the apex of the heart, because the pericardial sac is here anchored to its upper surface. Under ordinary conditions, therefore, the expansion of the lungs does not depend so much upon the actual descent of the diaphragm as upon the enlargement of the complementary space. Thus, it has been observed by

FIG. 239.—DIAGRAM SHOWING THE POSITION OF THE DIAPHRAGM AND ADJOINING WALL OF THE TRUNK ON INSPIRATION AND EXPIRATION.

E, expiration; J, inspiration. The diaphragm moves downward and the walls of the trunk outward, increasing the size of the complementary space C. The slight depression at H is caused by the apical portion of the heart.

means of the Röntgen rays that the vertical diameter of the chest is increased by only 10 mm. in the central area of the diaphragm, and while forced inspiration gives rise to a somewhat greater descent (12 to 14 mm.), the real purpose of diaphragmatic respiration seems to be to draw the inferior borders of the lungs into the complementary space and to act upon the lower areas of these organs. Their upper areas are also expanded, but in a much smaller measure. On this account, pleuritic adhesions are more likely to form in the upper recesses of the intrapleural space, and catarrhal and tuberculous infiltrations are particularly liable to affect the more poorly ventilated tips of these organs.

As the diaphragm descends, it pushes the neighboring abdominal viscera downward,¹ but their displacement is only made possible by the outward bulging of the anterior and lateral abdominal walls. In this way, the contracting diaphragm places the latter under a certain elastic tension. In other words, its muscular energy is temporarily transformed into potential energy which is again made use of during the succeeding expiration in forcing the abdominal viscera and overlying diaphragm back into their original position. It need scarcely be emphasized that the direct mechanical effect of this movement is far reaching, because it favors not only the venous return from the posterior extremities and organs of the abdomen but also that from the anterior parts of the body.² In addition it exerts an important influence upon the flow of the lymph and bile. It should also be remembered that the "aspiratory power of the thorax" which is responsible for the negativity of the venous blood pressure, may in large part be ascribed to the activity of the diaphragm.

In lean persons the movements of this septum are frequently indicated upon the external surface of the chest by a furrow-like depression, the so-called *linea diaphragmatica*, which progresses wave-like over the lower intercostal spaces. In as much as this retraction follows in the wake of the contracting muscular brim of the diaphragm, it is indicative of the strength of the aspiration and of the force with which the atmospheric pressure tends to push the thoracic wall of this region inward. This retraction may be made to appear in almost any person by forcing the respiratory movements. It is also of interest to note that the contractions of the diaphragm are prolonged, simulating the "tetanic" contractions of striated muscle tissue when subjected to a quickly interrupted current of brief duration.³ Clearly, this mode of contraction, which insures the fullest

¹ The earlier conception, that the pleural cavity is filled with air and that the lungs contract actively, was proved to be erroneous by Haller, his evidence being based upon observations of the movements of the diaphragm and adjoining pulmonary tissue made through the thinned tissue of the lower intercostal space. See: *De diaphragmate*, Göttingen, 1741.

² Burton-Opitz, *Am. Jour. of Physiol.*, xxxvi, 1914, 64.

³ Markwald, *Zeitschr. für Biol.*, xxiii, 1887, 149.

possible expansion of the lungs, points toward a certain difference in the structure or constitution of the diaphragmatic myoplasm.

The *increase in the anteroposterior and transverse diameters* of the chest is effected in the following manner: Posteriorly, the heads of the different ribs are in articulation with the vertebral column forming here partially movable joints. Anteriorly, on the other hand, the first ten pairs of ribs are anchored to the sternum by the costal cartilages, the upper seven of them being connected with this bone directly and the lower three indirectly, while the eleventh and twelfth pairs of ribs remain free and functionally constitute a part of the abdominal wall. When at rest, the different ribs incline obliquely downward and forward, so that their anterior extremities come to lie at a lower level than their posterior. During inspiration they are elevated and rotated outward, this movement being made possible by the flexibility of the costal cartilages and the yielding character of the costochondral and chondrosternal articulations. It is evident that the lessening of the obliquity of the ribs increases the distance between the sternum and the spinal column; moreover, inasmuch as the different pairs of ribs form rings, the diameters of which steadily increase from above downward until the seventh pair has been reached, it necessarily follows that their elevation also increases the breadth of the thorax. Thus, the seventh rib is raised to the level previously occupied by the sixth, and the sixth to that of the fifth, and so on until the first has been reached. In addition, it is to be noted that the elevation of the ribs is associated with a slight outward rotation at their angles. This may be gathered from the fact that their external surfaces are turned outward and downward on expiration, and directly outward on inspiration. This rotation alone is sufficient to increase the transverse diameter of the chest.

Each rib articulates with the spinal column in two places. Its head lies in contact with the body of the vertebra and its tubercle with the transverse process. In moving upward the different ribs rotate around an axis drawn through these two points, but inasmuch as their shafts are directed obliquely downward on expiration, their elevation during inspiration forces their sternal ends farther outward and away from the spinal column. Although this movement is greatly restricted, because the ribs are not freely movable upon the sternum, these articulations are rendered more yielding by the interposition

FIG. 240.—DIAGRAM TO ILLUSTRATE THE EFFECT OF THE SLANT OF THE RIBS.

S, the spinal column; *a*, the position of the rib in normal expiration; *a'* its position (exaggerated) in inspiration. The distance between the spinal column and the sternum (*st.*), *i.e.*, the anteroposterior diameter of the chest is increased). (*American Text-book of Physiology.*)

of the costal cartilages. During inspiration these cartilaginous segments are subjected to an eversion and slight torsion.

The Inspiratory Movement.—It need scarcely be emphasized that the space which is added to the thoracic cavity during inspiration, is immediately taken up by lung tissue. In this way the more fully expanded organs are capable of accommodating that extra amount of air which is required for the oxidative processes of the body. As has been stated above, the inspiratory movement is participated in by a number of muscles which are designed as the *muscles of inspiration*. They are classified further as *intrinsic* and *extrinsic*, because some of them are actual constituents of the walls of the thorax, while others arise elsewhere and are merely attached to its framework. Furthermore, inasmuch as many of these muscles are brought into play only during forced or labored respiration, it is customary to divide them into *normal* and *accessory muscles* of inspiration.

FIG. 241.—SIXTH DORSAL VERTEBRA AND RIB. (Reichert.)

As normal muscles of inspiration are to be regarded the diaphragm, the intercostales externi and the serratus posticus superior, and as accessory muscles the scalenus anticus, medius et posticus, the sternocleidomastoideus, trapezius, pectorales major et minor, rhomboides major et minor and serratus anticus. The levatores costarum longi et breves, which are sometimes classified under the first heading, do not participate in the raising of the ribs and belong to the

muscle system of the vertebral column.¹

Under ordinary conditions, the action of the normal muscles of inspiration is adjusted in such a way that the diaphragm assumes a preponderating rôle; in fact, this muscle alone almost suffices to carry on a proper interchange of the gases as long as the body is only moderately active. But when an additional supply of air is needed, other muscles are brought into play; the lower intercostals being activated first, and subsequently the upper intercostals and accessory muscles. In this way, the previously *diaphragmatic* or *abdominal* type of respiration is converted into the *costal* type. Hutchinson² states that in abdominal breathing the abdomen is seen to bulge out before the thorax is moved upward, while in costal breathing the elevation of the ribs occurs first.

¹ Du Bois-Reymond, *Ergebn. der Physiologie*, ii, 1902, 387.

² Todd's *Cyclopædia of Anatomy and Physiology*, 1849.

Under ordinary conditions, however, these terms are used only in a relative way to indicate whether the diaphragm and lower intercostals or the upper costal and intercostal muscles are the chief factors in respiration. It is customary to state that the respiration in men is diaphragmatic, while that of women is costal.¹ By some investigators this greater mobility of the thorax in the female is regarded as a sexual characteristic, while others hold that it is the artificial result of a long-continued constriction of the waist and encasement of the abdomen. If regarded as a sexual characteristic, it may be said to protect the developing fetus against an undue intra-abdominal pressure, and to help the mother in retaining her normal respiratory capacity. The more recent investigations, however, do not uphold this view, because it has been shown that Indian and Chinese women, who have never worn corsets, show the abdominal type of breathing.² This is also true of white women who have not been in the habit of wearing tight-fitting clothes or have discarded the corset in later years. Thus, while it seems certain that the preponderance of costal breathing in woman does not possess a physiological basis, gestation no doubt throws the burden of respiration temporarily upon the thorax, until at the end of this period the play of the diaphragm can again go on unhindered. In visceroptosis the action of the diaphragm is greatly restricted and costal breathing is brought into play more and more.

In some animals the diaphragm presents a rounded outline and its tendinous portion is placed in the center between the sternum and the vertebral column. In others it is arranged bilaterally, its antero-posterior diameter in the region of the sternum being shorter than its transverse or oblique diameter. Each half is innervated by the corresponding phrenic nerve which arises from the third and fourth cervical spinal nerves and passes downward through the thorax in close proximity to the heart. The division of one of these nerves is immediately followed by a paralysis of the corresponding half of the diaphragm, while the division of both nerves gives rise to a uselessness of the entire muscle. The latter procedure generally proves fatal, and especially in young animals, because the respiratory interchange then becomes wholly inadequate. In this connection mention might also be made of the fact that the quiescent diaphragm contracts at times synchronously with the heart. This phenomenon, which may be obtained with the chest open or closed, seems to require a certain high degree of nervous excitability, either local or general. The action

FIG. 242.
—DIAGRAM
SHOWING THE
ENLARGEMENT
OF THE TRUNK
ON NORMAL
(DIAPHRAGMA-
TIC) AND FOR-
CED (COSTAL)
RESPIRATION.

¹ Hasse, *Archiv für Anatomie*, 1903, 23.

² Fitz, *Jour. of Exp. Med.*, i, 1896.

current arriving in the ventricles is then propagated to the left phrenic nerve, because this nerve lies in close contact with the cardiac apex. Moreover, as the diaphragmatic muscle reacts more quickly than the ventricular, the former is generally seen to twitch before the systole of the ventricles has fully developed.¹

The Action of the Intercostal Muscles.—The ribs are connected with one another by two sets of muscles, known as the intercostals. The *external intercostals* extend obliquely downward and forward, their attachment upon the rib above being nearer the spinal column than their insertion upon the rib below. The *internal intercostals* pass in the opposite direction, their place of attachment upon the rib below being nearer the spinal column than their insertion upon the rib above. The action of these muscles may readily be deduced from the adjoining schema (Fig. 243) if it is remembered that a contracting muscle causes its point of insertion to move closer to its point of attachment. If

FIG. 243.—DIAGRAM ILLUSTRATING THE ACTION OF THE INTERCOSTAL MUSCLES.

S, sternum; V, vertebral; A and B two consecutive ribs; EE_1 , external intercostal muscle; JJ_1 , internal intercostal muscle. The contraction of the first raises the ribs (II), while the contraction of the second lowers them (III). The distance SV is now shortened.

A and B represent two consecutive ribs, the posterior extremities of which are movable upon the vertebral column, but relatively immovable upon the sternum, the line E to E_1 indicates the direction of the external intercostal fibers and the line J to J_1 that of the internal intercostal fibers (Fig. 243, I). If the first muscle is now made to contract, the ribs assume the position shown in Fig. 243, II, because the distance between the two ends of the different external intercostal fibers has been shortened. This muscle, therefore, elevates the ribs and is inspiratory in its action. If the second muscle is now made to contract, J is brought nearer to J_1 and the ribs are depressed (Fig. 243, III). The internal intercostals, therefore, are expiratory in their function.

A similar but more elaborate representation of the action of the intercostal and intercartilaginous² muscles has been given by Hamberger, in 1727, but the

¹ Pike, Am. Jour. of Physiol., xl, 1916, 433.

² The musc. intercartilaginei constitute that part of the musc. intercostales interni which is situated between the costal cartilages.

correctness of this explanation has been questioned by A. v. Haller, who regarded both intercostals as inspiratory in their function. As is indicated in Fig. 244, two bars are arranged in such a way as to represent two adjoining ribs (*A* and *B*) suspended from the vertebral column and united in front with the costal cartilages *a* and *b*, and the sternum (*S*). The external intercostal and intercartilaginous muscles are represented by rubber bands, placed in the position *E* and *E*₁, and *J* and *J*₁ respectively. If, to begin with, the parallel bars are depressed sufficiently to place the rubber bands under elastic tension (Fig. 244, *I*), their release is immediately followed by an upward movement (Fig. 244, *II*) for the reason that the elastic forces, although acting in opposite directions, are equal, and as they are exerted in a parallelogram, the component acting upward on the long arm of the lever exceeds the component acting downward on the short arm of the lever. Moreover, as the distance between the consecutive ribs is fixed, their upward movement must increase the angle between them and the costal cartilages, and must also lead to a forward movement of the sternum.

FIG. 244.—DIAGRAM ILLUSTRATING THE ACTION OF THE EXTERNAL INTERCOSTAL AND INTERCARTILAGINEI MUSCLES.

V, vertebral column; *S*, sternum; *AB*, two consecutive ribs; *ab*, their costal cartilages; *EE*₁, external intercostal; *JJ*₁, intercartilaginei muscles; *I*, position at end of expiration, when these muscles are under tension; *II*, position at end of inspiration when these muscles have contracted, raising the ribs and pushing the sternum forward.

While the action of the external and internal intercostal muscles has been a subject of much controversy, it is commonly held to-day that the former elevate and the latter depress the ribs. For this reason, the external one should be classified as an inspiratory, and the internal one as an expiratory muscle. It is to be noted, however, that they are not activated at the same time, because those placed between the lower ribs serve as an aid to the diaphragm and are seldom at rest, whereas those situated between the upper ribs remain inactive for long periods of time until a fuller expansion of the lungs is required. Besides, it should not be forgotten that the intercostal muscles serve as tensors of the intercostal spaces. As Landois¹ has shown, if the soft parts between the ribs were perfectly flabby, they would be pulled inward by the elastically recoiling lung, and more markedly so during the inspiratory movements. Obviously, the alternate contraction of these muscles prevents this belying inward during practically the

¹ *Lehrbuch der Physiol.*, i, 1909, 190.

entire respiratory cycle and keeps the lungs in the fullest possible state of expansion. Moreover, their action as tensors immediately assumes a much greater functional importance if the respiratory motions become forced or if the intrathoracic pressures are momentarily greatly increased or decreased. Conditions of this kind arise, for example, during the acts of coughing and sneezing and during sudden inspiratory efforts, such as are required during speaking and singing. At this time the contracting intercostal muscles actually protect the thorax and its contents against injury, just because they prevent the outward and inward bellying of its intercostal septa.

The Expiratory Movement.—Expiration, as has been stated above, is largely a passive process in which three factors play a part, namely gravity, the recoil of the stretched tissues, and muscular activity. Inasmuch as the thorax is raised during inspiration, there must be present a tendency on the part of the ribs, sternum and soft structures to resume their former position on account of their weight. This factor, however, cannot make itself felt until the muscular force acting upon them during inspiration has been made to cease. This is also true of the elastic recoil of the soft and hard parts constituting the thoracic wall, and naturally, this factor makes itself felt in two ways. On the one hand, we have the recoil of the lungs upon which the preceding inspiratory movement has forced a condition of hyperexpansion, and, on the other, the recoil of the cartilaginous and bony constituents of the thorax which by the same means have been placed under a considerable elastic tension. These conditions must necessarily augment one another, because the direction of their action is toward the center of the thorax. The only muscle which participates in the expiratory movement is the internal intercostal, but since quiet breathing is effected very largely by the diaphragm alone, it is doubtful whether much importance can be attached to its action. At best, solely the lowermost rows of this muscle would be called into play. Various conditions, however, may arise in which the elastic forces must be promptly and efficiently assisted by this muscle and possibly also by the *triangularis sterni*. The latter, in all probability, depresses the cartilages and anterior extremities of the ribs. As far as the capacity of the thorax is concerned, the three factors just enumerated unite to decrease it along the anteroposterior and transverse planes.

Essentially the same factors take part in decreasing the vertical diameter of the chest. To begin with, the descent of the diaphragm places the abdominal viscera under pressure with the result that the anterior and lateral walls of the abdomen are forced outward and are put on the stretch. Below, the diaphragm meets with the resistance of the pelvic floor, and posteriorly with that of the vertebral column. Thus, it is commonly noted that this outward movement is also participated in by the floating ribs and the lowermost true ribs, but a pronounced outward bulging of the thoracic-abdominal junction cannot result unless the downward progression of the diaphragm is

greatly hindered. A condition of this kind is commonly obtained during pregnancy or when the thighs are flexed upon the abdomen. In the nature of things, gravity cannot play a rôle in the upward movement of the diaphragm unless the body be placed in a position directly favoring this factor. The elastic recoil of the tissues, on the other hand, is of paramount importance. In endeavoring to regain its normal position, the stretched abdominal wall pushes the viscera and overlying diaphragm upward. At this very moment the upper surface of this now perfectly passive membrane is directly exposed to the elastic recoil of the lungs. It will be seen, therefore, that the diaphragm is made to assume its former position by two forces applied simultaneously to its under and upper surfaces. The elastic recoil of the abdominal wall pushes it upward, while the elastic recoil of the lungs pulls it upward.

In forced expiration the capacity of the thorax is decreased still further by the contraction of several abdominal and thoracic muscles. Besides the internal intercostals and the triangularis sterni, mention should be made at this time of the abdominales, serratus posticus inferior, and quadratus lumborum. Obviously, the latter augment the power of the recoil so that the abdominal organs are pushed against the inferior surface of the diaphragm with an even greater force than during normal expiration.

Accessory Movements of Respiration.—The muscles to which reference has just been made, are concerned with the respiratory variations in the capacity of the thoracic cavity and hence, with the expansion of the lungs. Besides these a number of other muscles might be mentioned which give rise to certain associated respiratory movements of the nostrils, pharynx and larynx. Thus, it may be noticed that the orifices of the external nares are dilated during inspiration and constricted during expiration. The former movement is produced by the contraction of the elevators of the alæ of the nose, while the latter is the result of the elastic recoil of these parts. Obviously, the purpose of this movement is to lessen the resistance to the inflow of air. A similar rhythmic widening of the respiratory passage occurs in the larynx, where the vocal cords are placed in the path of the current of air for purposes of phonation. The space between their free edges, the glottis, is enlarged during inspiration and narrowed during expiration. The former effect is dependent upon the contraction of the posterior crico-arytenoid muscles which abduct the tips of the arytenoid cartilages to which the posterior extremities of the vocal cords are attached. The muscles of the neck and face may be made to contract rhythmically by rendering the respiratory movements more labored (dyspnea). It is also claimed that the caliber of the bronchi is increased during inspiration and decreased during expiration.

Classification of the Respiratory Muscles.—The preceding discussion, no doubt, has shown that it is difficult to give a perfectly

accurate classification of the muscles which take part in the expansion of the lungs. The following table, however, may serve as a general guide.

A. Inspiration.

1. Normal.

Diaphragm (nerv. phrenicus).

Musc. intercost. externi et intercartilaginei (nerv. intercostales).

2. Forced.

a. Muscles of the Trunk.

Musc. scaleni (nerv. plex. cerv. et brachialis).

Musc. serratus posterior superior (nerv. intercostales).

Musc. serratus anterior magnus (nerv. thor. longus).

Musc. pectoralis major et minor (nerv. thor. ant.).

Musc. sternocleidomastoideus (nerv. accessori).

Musc. trapezius (nerv. accessori).

Musc. extensores columnæ vertebralis (ram. post. nerv. dors.).

Musc. rhomboidei (nerv. dors. scapulæ).

Musc. levator scapulæ (nerv. dors. scapulæ).

b. Larynx.

Musc. sternohyoideus (nerv. ram. disc. hypoglossi).

Musc. sternothyreoideus (nerv. ram. disc. hypoglossi).

Musc. cricoarytenoideus (nerv. lar. inferior).

c. Pharynx.

Musc. levator veli palatini (nerv. facialis).

Musc. azygos uvulæ.

Musc. constrictores pharyngis (nerv. glossoph. et vagus).

d. Face.

Musc. dil. narium ant. et post. (nerv. facialis).

Musc. levator alæ nasi (nerv. facialis).

B. Expiration.

1. Normal.

Gravity and elastic recoil of the lungs, intercostal cartilages and abd. muscles.

2. Forced.

Musc. intercostales interni (nerv. intercostales).

Musc. abdominales.

Musc. triangularis sterni (nerv. intercostales).

Musc. serratus post. inferior (ram. ext. nerv. dors.).

Musc. quadratus lumborum (ram. musc. e plexa lumbali).

CHAPTER XXXVIII

THE FREQUENCY AND CHARACTER OF THE RESPIRATORY MOVEMENTS

Methods of Recording the Respiratory Movements.—The early measurements of the diameter, of the thorax made with the help of a tape-measure and large calipers, were soon superceded by the registration of the movements of the chest by means of levers placed horizontally upon its external surface,¹ or by means of an instrument

¹Vierordt and Ludwig, Arch. für physiol. Heilkunde, xiv, 1855, 253, and Riegel, Die Athembewegungen, Würzburg, 1873.

modeled after the sphygmograph. A very simple *stethograph* may be made by applying an ordinary rubber bulb to the surface of the chest by means of a tape and by connecting its orifice with a recording tambour. Marey¹ has advocated the use of a rubber tube closed at its ends and fastened around the chest. This tube is connected by means of a cannula with a recording drum which then responds to the changes in pressure caused by the respiratory movements. Later on this *pneumograph* took the form of a metallic tambour placed directly over a narrow plate of steel. When properly applied to the surface of the chest, the respiratory movements subject this plate to different degrees of tension which are transferred by a lever to the rubber membrane of the tambour (Fig. 245). Another method frequently practised is to register the variations in the intrapleural pressure by means of a tambour connected with the intrapleural space. In a similar way, the intrathoracic pressure may be recorded with the help of a tambour connected with a catheter which is passed down the

FIG. 245.—DIAGRAM OF MAREY'S PNEUMOGRAPH.

The instrument consists of a tambour (*t*), mounted on a flexible metal plate (*p*). By means of the bands *c* and *c* the metal plate is tied to the chest. Any increase or decrease in the size of the chest will then affect the tambour by the lever arrangement shown in the figure. These changes in the tambour are transmitted through the tube *r* as pressure changes in the contained air to a second tambour (not shown in the figure) which records them upon a smoked drum. (*American Text-book of Physiology*.)

esophagus until its free end comes to lie a short distance above the diaphragm. It is also possible to insert a T tube in the trachea and to connect its lateral branch with a recording tambour, or to permit the animal to respire through a large bottle, one of the outlets of which communicates with a recording instrument. If the abdomen has been opened, the diaphragm may be connected with a writing lever by means of a small hook and thread acting over a pulley. It has also been advocated to separate the ensiform cartilage from the manubrium of the sternum and to attach it by means of a thread to an ordinary writing lever.

Pneumatogram.—A record of the respiratory movements consists as a rule of a series of waves composed of alternate upstrokes and downstrokes, but whether the inspiratory period is represented by the ascending limb or by the descending limb depends upon the manner of action of the recording instrument. Thus, Marey's pneumograph acts aspiringly, pulling the lever of the recording tambour downward

¹La méthode graphique, Paris, 1873; also see: Brondgeestsche, Onderzoek, g. i. h. physiol. Lab., Utrecht, ii, 1873, 326.

during inspiration, while an ordinary rubber bulb yields a positive pressure during this period, and forces the writing lever upward.

The inspiratory movement sets in gradually. It acquires a considerable speed in its intermediate phase but again becomes slow toward its end. Expiration is slow at first, rather rapid in its intermediate phase and decidedly slow toward its end. In general, therefore, inspiration sets in more abruptly than expiration and occupies a somewhat shorter time than expiration, the relationship between these periods being as 10:14. Furthermore, while the expiratory movement follows immediately upon the completion of inspiration, the next inspiratory motion is not begun until a few moments later. It is to be noted, however, that a true pause is not developed at this time in spite of the fact that the muscles are perfectly quiescent. This must necessarily be so, because the elastic forces are at play even during this interim of relative "rest," tending to retain the chest in a semi-active or "set" condition. It is also a matter of common experience that the action of the respiratory muscles may be arrested at

FIG. 246.—PNEUMATOGRAM RECORDED BY CONNECTING THE INTRAPLEURAL SPACE WITH A MEMBRANE MANOMETER.

J, Insp. movement; *E*, expir. movement. The figures indicate the negative pressure recorded during these resp. cycles.

any time during the respiratory cycle. Ordinarily, however, the desire to resume this activity becomes imperative in less than a minute, owing to the accumulation of excessive amounts of carbon dioxide. But if the system is first thoroughly ventilated and surcharged with oxygen by a series of forced respiratory movements, the breath may be held for a much longer period of time. Professional divers, for example, are capable of remaining under water for several minutes.

The number of respirations in a given period of time vary with the conditions under which the animal lives. In the adult human being from 16 to 20 cycles are completed in the course of one minute, their average number being 18. It is also to be noted that the respiratory frequency is greater when the person assumes the erect position than when recumbent or sitting down. Naturally, this change is in accordance with the oxygen requirement, the mere act of rising necessitating a greater muscular activity and metabolism. An important influence is also exerted by age, as may be gathered from the following compilation:

	Respirations in a minute
New-born	62
0- 1 year.....	44
5-15 years.....	26
15-20 years.....	20
20-25 years.....	18.7
25-30 years.....	15
30-50 years.....	17

The fact that the respiratory frequency varies in accordance with the intensity of the metabolism may be proved in several ways. Thus it is readily noticed that muscular exercise and glandular activity increase it, while sleep diminishes it.¹ A heightened respiratory activity is usually associated with rises in the temperature of the body or of the surrounding air (heat dyspnea). A similar effect is produced by increases in the barometric pressure and in the carbon dioxide content of the inspired air. The frequency of respiration and the size of the animal preserve an indirect relationship to one another, because the smaller animals possess a more extensive body-surface in relation to their mass than the larger ones, and hence, suffer a much greater loss of body-heat. This greater dissipation necessitates a more rapid production of heat, *i.e.*, a more active metabolism. The latter is invariably characterized by a greater respiratory frequency.²

The wide differences noted in different species are made apparent by the following table:

Horse.....	6-10
Ox.....	10-15
Sheep.....	12-20
Dog.....	15-25
Pig.....	15-20
Man.....	16-24
Cat.....	20-30
Pigeon.....	30
Rabbit.....	50-60
Sparrow.....	90
Guinea-pig.....	100-150
Rat.....	100-200

The rhythm of respiration is also disturbed by emotions and during the production of sounds, such as are used in speaking. In health a fairly constant ratio of 1 : 4 is maintained between the rate of respiration and that of the heart. It is also true that this ratio is frequently retained even under pathological conditions, because the respiratory and cardiac activities are subject to practically the same influences and react toward them in an almost identical manner.

The Changes in the Position of the Lungs.—The expansion of the lungs gives rise to a change in their volume and hence, also in their

¹ Chait, Dissertation, Zürich, 1907, Dohrn, Zeitschr. für Geburtsh., xxxii, 1895, 25, and Recklinghausen, Pflüger's Archiv, lxii, 1896, 451.

² Johanson, Skand. Archiv für Physiol., 1895, 20.

position within the thoracic cavity. Posteriorly, these organs meet with the resistance of the vertebral column, and above, with that of the structures situated at the base of the neck. Centrally, their enlargement is opposed by the heart and large blood-vessels. For this reason, they seek in general a downward and outward course, their roots moving downward and forward and their anterior margins downward and inward. These changes enable their borders to move closer together. Their exact boundaries may be made out at any time by the method of *percussion* which consists in holding a thin plate of rubber firmly against the external surface of the chest and in sharply tapping upon it with a small bolstered hammer (Piorry's pleximeter). A more convenient procedure is to apply the third finger of the left hand to the chest and to strike it with the bent second or third finger of the right hand. The sound elicited in this way varies with the nature of the subjacent tissues. If the lung tissue underneath is fully expanded, a clear resonant sound is evoked. Consolidated lung tissue, on the other hand, imparts a dull character to this sound, while partly infiltrated tissue gives rise to intermediate notes. The same holds true if the layer of the subjacent pulmonary tissue is thin.

Anteriorly, the apices of the lungs are situated 3-7 cm. above the clavicle, and posteriorly, at about the level of the seventh spinous process. When held in the expiratory position, their lower borders extend in front from the upper edge of the sixth rib obliquely downward to the level of the tenth rib at the back of the chest. A deep inspiration forces this boundary downward until it rests in front, opposite the seventh rib and behind, opposite the eleventh rib. Quite similarly, a forceful expiration allows their lower boundary to ascend to about the next ribs above those mentioned previously. Complete dullness prevails in the region of the heart, but the size of this area differs with the degree of expansion of the lung. When in the expiratory position, the anterior border of the left organ remains at some distance from the midsternal line, thereby increasing the cardiac dullness until it embraces a triangular space which is limited by the left border of the sternum, the fourth costosternal articulation and the sixth costal cartilage. In a robust man whose arms are held in the horizontal position, the circumference of the chest at the level of the nipples measures 82 cm. on expiration and 89 cm. on deep inspiration. At the level of the ensiform cartilage these measurements are 76 cm. and 83 cm. respectively. In infants and old people, however, the circumference of the lower part of the thorax is usually greater; moreover, the right side of the adult is prone to be larger than the left on account of its greater muscular development.

Respiratory Sounds.—If the ear is applied to the chest over perfectly sound lung tissue, a soft rustling sound is heard during inspiration which is designated as the vesicular murmur. It is thought to arise either in the alveoli or at the point where the bronchiolar terminals open into the much larger infundibula. Obviously, its cause

must be sought in the sudden distention of the air vesicles and the flow of the air through the fine bronchioles into the enlarged infundibula. The coincidence that this murmur is especially distinct in children, is referable to the smaller caliber of their infundibular spaces. Furthermore, the quality of this sound is generally modified by the noises which are set up by the air as it rushes through the trachea and bronchi. They are transmitted from here to other regions of the pulmonary parenchyma. For this reason, the general vesicular murmur is usually regarded as being due to two causes, namely, to the true vesicular sound produced in the infundibula, and the glottic sound, generated by the current of air as it traverses this aperture. Consequently, the more remote regions of the lung give rise to a vesicular sound of purer quality than those situated nearer the larynx. In large animals, in fact, this resonant element fails to be transmitted to the more distant pulmonary tissue and can only be heard in the regions adjacent to the bronchioles. It is possible to destroy the glottic element of the murmur entirely by permitting the animal to breathe through an opening in the trachea.

On listening over the larynx, trachea or bronchi, either with the unaided ear or with a stethoscope, a loud blowing noise is heard during inspiration as well as during expiration. It is called the *bronchial murmur*. During health this sound is not audible over the outlying districts of the lung, but is propagated into these regions if the alveoli are deficient in air. A condition of this kind arises quite commonly from compression of the pulmonary parenchyma or in consequence of exudations of inflammatory material (pneumonia) and hence, bronchial breathing over any part of the lung other than that adjoining the larger air-tubes is always indicative of consolidation of this tissue. It might also be mentioned that the absence of these sounds does not necessarily imply that the underlying lung tissue is not being expanded, because the sounds may be prevented from reaching the ear by fluid effused into the pleural cavity (pleurisy).

The Changes in the Intrathoracic, Intrapulmonic and Intra-abdominal Pressures.—It has previously been shown that the recoil of the stretched tissue of the lungs sets up a pressure in the intrapleural and mediastinal spaces which is negative to that inside the respiratory passage. Knowing its cause, it may justly be assumed that the inspiratory enlargement of the chest increases this negativity still further, because the lungs are subjected to a somewhat greater elastic tension during this period. The expiratory movement, on the other hand, diminishes the elastic pull of these organs, and hence, also the *intrathoracic pressure*, *i.e.*, it permits the pressure to approach that of the atmospheric air or zero-line. These changes may be followed more closely by connecting the intrapleural space with a water manometer in the manner previously described. With the chest in the static position the intrapleural pressure amounts to about -5 mm. Hg, *i.e.*, to 760 mm. Hg atmospheric pressure minus 5 mm. Hg produced

by the elastic recoil of the lung tissue, which equals 755 mm. Hg. During quiet inspiration it attains a value of -9 mm. Hg and during forced inspiration a value of as much as -30 or -40 mm. Hg.

The *intrapulmonic pressure* pursues a similar course. It falls during inspiration and rises during expiration, but remains always above the former. As the chest is expanded, the pressure in the pulmonary passage falls below that of the air without, initiating a rapid inflow of air which does not cease until an equalization has been effected. Quite similarly, the expiratory movement places the air in the respiratory passage under a pressure higher than that of the atmosphere, and gives rise to an outflow of air which does not cease until the pressures have been equalized. It need scarcely be mentioned that the cause of these changes in the intrapulmonic pressure is to be sought in the resistance encountered by the air in its passage through the relatively narrow tracheal communication, and especially in its flow

FIG. 247.—REPRESENTING THE CHANGES, 1, IN THE INTRAPULMONIC, AND 2, IN THE INTRA-THORACIC PRESSURE DURING INSPIRATION AND EXPIRATION.

through the glottis. Quite naturally, any condition which lessens the lumen of the upper portion of the respiratory passage, must tend to augment these variations in the intrapulmonic pressure. It must also be evident that these changes may be intensified by breathing more forcibly. Under ordinary conditions, however, the inspiratory fall in intrapulmonic pressure amounts to only 1.5 mm. Hg, while its expiratory rise rarely exceeds 2.5 to 3 mm. Hg. During forced respiration much higher values are obtained. Donders, for example, was able to cause a fall of 57 mm. Hg and a rise of 87 mm. Hg, the pressure being registered in this case by a manometer which was connected with one nostril, while the other was held shut.

The *intra-abdominal pressure* is registered by inserting a hollow probe among the superficial coils of intestine and connecting its free end with a water manometer. During quiet respiration it retains a value very close to zero,¹ but naturally, the active participation of

¹ Emerson, Archiv of Int. Medicine, vii, 1911, 1.

the abdominal muscles in expiration gives rise to much higher values. This is also true of those expiratory blasts of air which are made use of in speaking, singing, coughing, and sneezing. Inasmuch as the peritoneal cavity contains no air, the individual organs are packed closely together. By closing the glottis and simultaneously contracting the diaphragm and abdominal muscles, they may be subjected to a considerable pressure, which greatly aids in the expulsion of the feces and urine. This action, which is commonly designated as the "abdominal press," also constitutes an important factor in childbirth.

Quantitative Determination of the Respired Air.—The volume of air which is taken into our lungs during a given period of time, varies with the respiratory needs of our body. Obviously, a much greater quantity of air is required when the tissues are active than when they are inactive. But while the extent and frequency of the respiratory movements may serve at any time as an indication of the intensity of the gas interchange, a direct volumetric determination of the air respired is only possible by calibration. The instrument used for this purpose is known as the *spirometer*. The one devised by Hutchinson¹ is a modified gasometer (Fig. 248). It consists of a cylindrical receptacle (*B*) filled with water, in which is suspended a second cylinder (*A*) containing air. The latter is counterbalanced by weights (*G*) in such a manner that it may be made to move with the least possible resistance. The tube (*C*) enters through the outside cylinder, and is continued upward to a level above the surface of the water in the inside compartment. If air is expired through this tube, the inside cylinder rises a certain distance out of the water, while if air is inspired through it, the cylinder sinks to a lower level. The amounts of air added or subtracted in this way are indicated by a pointer upon a neighboring centimeter scale.

In order to be able to determine the volume of the air breathed in the course of a long period of time, it is necessary to know two factors, namely, the average frequency of the respiratory movements and the average volume of air respired each time. It is also possible to solve

FIG. 248.—WINTRICH'S MODIFICATION OF HUTCHINSON'S SPIROMETER. (Reichert.)

¹ Med.-chirurg. transact., xxix, 1846, 137.

this problem with the help of Gad's pneumatograph¹ which consists of a square box with double walls, the space between them being filled with water (Fig. 249). The cover of this air-chamber is fastened with hinges on one side, but is freely movable along its other three sides. If air is breathed from or into its central compartment, the cover moves down or up, its excursions being registered upon the paper of a slowly revolving kymograph.

Quantities of Air Respired.—A full grown man inspires and expires about 500 c.c. of air with each respiratory act, the expiratory volume being slightly larger on account of its expansion by heat. This is called the *tidal air*. By the deepest possible inspiration an additional quantity may be accommodated which amounts to at least 1600 c.c. This is the *complemental air*. Quite similarly, the most forcible expiration relieves the lungs of about 1600 c.c. of air in addition to the 500 c.c. of tidal air. This amount is designated as the *supple-*

FIG. 249.—GAD'S PNEUMATOGRAPH.

mental air. It is to be noted, however, that even the most forcible expiratory effort does not empty the lungs completely. A certain quantity is always left behind, because the lungs do not collapse even during forced expiration, but remain in a condition of partial distention. This air, which cannot be expelled normally, is the *residual air*. Its amount has been estimated at 1000 to 1200 c.c.² Its function, obviously, is to prevent the alveolar walls from collapsing, because in this eventuality very much greater muscular efforts would be required to subject these cells again to a normal degree of inspiratory distention. Furthermore, it must be evident that this partially expanded condition of the lungs favors a free movement of the blood through the pulmonary capillaries. In this connection brief reference should also be made to the fact that the residual air cannot be removed in its entirety even by opening the thorax and by permitting the lungs to collapse. Neither can this end be attained by exerting a gentle pressure upon the surfaces of the excised organ, because the walls

¹ Archiv für Anat. und Physiol., 1879, 181. Modifications of this spirometer have been constructed by Durig (Zentralbl. für Physiol., xvii, 1904, 258), Gutzmann (Mediz. Klinik, 1910), and Zwaardemaker (Archiv intern. de laryngologie, 1906).

² Jacobson, Pflüger's Archiv, xliii, 1888, 236.

of the small bronchial tubules have come together before the infundibula have been completely emptied. In this way a portion of the residual air has been entrapped in the different air cells. This constitutes the *minimal air*. It is possible to remove it, however by chemical means; for example, by displacing it with oxygen and carbon dioxid and bringing it in contact with water. A lung so treated ceases to float.

From the foregoing discussion it may readily be gathered that the reserve amount of air which is contained in the lungs at the end of a quiet expiration, following a quiet inspiration, amounts to about 2500 c.c. and consists of the residual and supplemental portions. It is designated as the *stationary air*. The term *vital or respiratory capacity* signifies the quantity of air which may be expelled from the lungs by the most forcible expiration after the deepest possible inspiration. It includes the tidal, complemental and supplemental portions and may, therefore, be estimated at 3700 to 4000 c.c. If to this quantity is added the residual air, the *lung capacity* is obtained, which in round numbers may be said to equal 5000 c.c. The term *bronchial capacity* refers to the quantity of air which is accommodated in the trachea and bronchi. It is generally estimated at 140 c.c. so that only 360 c.c. of the 500 c.c. of tidal air are actually forced into the deeper passages of the lungs.¹ What bearing this fact possesses upon the interchange of the gases will be seen later. While it is true that these figures allow us to draw definite conclusions regarding the respiratory power of an individual, no special clinical value can be attached to them, because they may be materially increased by practice and are subject to a number of conditions, such as posture, age, sex, race, and occupation. Mountaineers, for example, possess a greater respiratory capacity than the inhabitants of lowlands.

These data now permit us to compute the quantity of air respired by an adult person during a given period of time. Assuming that the respiratory frequency is 15 in a minute and that the tidal air amounts to 500 c.c., then 7.5 liters are breathed in a minute, 450 liters in an hour, and more than 10,000 liters in the course of a day. It is from this enormous quantity of air that the oxygen requirement of our tissues is satisfied.

Modified Respiratory Movements.—The rhythmical enlargement of the thorax has as its object the ventilation of the lungs so that a proper interchange of the gases may be had between the intrapulmonic air and the blood. Under certain conditions, however, the respiratory current of air is employed during brief periods of time for other purposes, this change generally necessitating a modification of either the inspiratory or expiratory movement. Acts of this kind are speaking, singing, coughing, sneezing, sighing, laughing, crying, sobbing, hic-cough, yawning, and snoring; in fact, if other species of animals are here taken into consideration, this list may be made to include a

¹ Loewy, Pflüger's Archiv, lviii, 1894, 416.

great number of noises and sounds, such as barking, neighing, purring, roaring, bellowing, bawling, whining, braying and growling.

Some of these reactions are voluntary in their nature, others involuntary; furthermore, while some of them are undertaken in consequence of a definite mental concept, others lack a central cause and are reflex in their character. In many cases the latter do not possess a local cause, but are the result of irritations in other parts of the body. Thus, coughing frequently arises from inflammatory reactions in the intestines, stomach, liver, ovaries or uterus, while hiccough is commonly associated with irritations in the stomach, liver or nerve centers. Being reflex in their character, it is possible at times to inhibit these reactions by setting up simultaneous afferent impulses. Sneezing, for example, may be prevented by firmly pressing the finger upon the upper lip, while the act of yawning may be inhibited by a sudden cutaneous stimulus.

As far as the respiratory movements are concerned, *coughing* may be defined as an interrupted expiration, the interruption being due to the partial closure of the glottis. But, in order that its purpose may be achieved, which, obviously, is the dislodgment of the irritating body from the respiratory passage, it is necessary to have an adequate supply of air on hand. For this reason, this action is commonly preceded by an inspiration. The air is then ejected through the mouth, the glottis being forced open by the abrupt compression of the intrapulmonic air in consequence of the contraction of the accessory muscles of expiration. *Sneezing* is accomplished in practically the same manner. In this particular case, however, the expiratory blast of air is forced through the nasal cavity, the glottis being widely opened, while the cavity of the mouth is shut off from that of the pharynx by the approximation of the base of the tongue to the soft palate. This act is also initiated by a deep inspiration. *Sighing* is a deep and prolonged inspiration. Brief, jerky inspiratory efforts, made with the mouth closed, constitute the act of *sniffing*. If the mouth and glottis are kept open, while the vocal cords are thrown into vibration by an expiratory blast which is repeatedly interrupted, the phenomenon of *laughing* results. *Crying* is differentiated from laughing by the rhythm of the movement and the position of the facial parts. *Sobbing* consists of a series of spasmodic inspirations, with partially closed glottis, which are followed by a prolonged expiration. *Hiccough* is produced by the spasmodic contraction of the diaphragm, the inspiratory motion being suddenly arrested by the closure of the glottis. In *yawning* a deep inspiration is taken with the mouth and glottis widely open; the succeeding expiration is short. *Snoring* results if the relaxed uvula and soft palate are thrown into vibration by the inflowing and outflowing air.

Artificial Respiration.—Conditions arise at times when it becomes necessary to maintain an adequate ventilation of the lungs by artificial means. The methods then commonly practised may be divided into two groups, namely, those devised to expand the lungs from without, as in normal breathing, and those effecting their rhythmic inflation through the trachea by air held under pressure. Artificial respiration is resorted to very frequently during laboratory experiments in order to allow us to open the chest without actually destroying the life of the animal. In other cases, it becomes imperative to ventilate the lungs artificially until the cause of the respiratory stoppage has been removed. For example, if an overdose of ether has been given, the prompt employment of artificial respiration generally serves to tide the animal over this period, because in most instances the heart does not cease to act until sometime after the stoppage of respiration. In fact, if this organ has already ceased to beat, it may

at times be reactivated by the prompt institution of artificial respiration, massage of the abdominal viscera and central blood-vessels, elevation of the posterior extremities, injections of adrenalin and other measures.

In animal experimentation artificial respiration meets with practically no difficulties, although its use upon human beings must necessarily remain restricted to the most favorable cases. Thus, it cannot yield beneficial results if the respiratory abeyance possesses a permanent pathological cause. Still, it cannot be doubted that it deserves a much wider application than is accorded it at the present time, when it is employed, and not always in a very scientific and efficient manner, in cases of drowning, asphyxiation by poisonous gases, and suspended animation from electrical shocks or pressure upon nerve

FIG. 250.—SHOWS THE POSITION TO BE ADOPTED FOR EFFECTING ARTIFICIAL RESPIRATION IN CASES OF DROWNING. (Schaefer.)

centers. Whatever the method employed, and whether in animals or man, artificial respiration must always be practised in closest imitation of the normal rate and depth of the respiratory movements. Too vivid a ventilation is almost as injurious as a subnormal one. Before the attempt is made to distend the lungs, the respiratory passage must be cleared of all obstructions, such as mucus and water. The mouth must be opened widely and the tongue drawn out so as to prevent its tip from becoming lodged behind the fauces. All tight clothing must be removed.

In imitating the normal expansion of the lungs, Sylvester proceeds as follows: The patient is placed on his back, with the head and shoulders supported upon a firm cushion somewhat above the level of the feet. The operator places himself at the patient's head, grasps the arms just above the elbows and draws them upward above the head. Having kept them in this position for two seconds, they are then pressed gently but firmly against the sides of the chest during an equal period of time. Calliano retains the arms in Sylvester's position, so that the thorax remains in the expanded condition continuously. He then presses at intervals of three seconds with the flat hands

against the sides of the thorax and epigastric region. This procedure may also be followed if the patient is placed in the supine position with his arms resting against the sides of his body. A method, which is commonly employed in the resuscitation of animals is the following: The body is raised free from the floor by the hind limbs. The mouth is opened and the tongue pulled out synchronously with the compression of the thorax which is effected by placing the flat hands from behind upon the sides of the lower part of the chest. Schäfer¹ suggests that the patient be placed in the prone posture, a heavy garment being placed underneath his chest and epigastrium. The operator assumes a kneeling position beside the legs of the patient and, bending forward, rests his flat hands against the sides of the lower part of the thorax, so that the tips of his thumbs come to lie close to the vertebral column. By gradually permitting his weight to be supported by his arms, the chest is pressed upon and air is forced out of the lungs. On releasing this pressure, the parts return into their original positions and cause the air to flow in.

The methods which purpose to distend the lungs with air held under pressure, are most commonly employed in long-continued experiments upon animals, but may also be used in resuscitating human beings. Thus, the expansion of the lungs of the new-born may be frequently facilitated by blowing air into these organs, the mouth of the operator being placed against that of the infant. In the laboratory, it is customary to expose the trachea of the animal and to insert in it a rectangular cannula which in turn is connected with a pair of bellows. In experiments of longer duration it is advantageous to employ a power pump which it is possible to regulate in such a way that a different rate and amplitude of respiration may be obtained within a few moments. The deflation of the lungs may be greatly hastened by the withdrawal of the air by slight suction.²

This principle is made use of in the construction of the so-called *pulmotor* or *lungmotor*,³ a small force-pump intended to be employed upon human beings. It is worked by hand and possesses safeguards in the form of adjustable valves. It may readily be surmised that the method of inflation through the mouth cannot present any unusual difficulties in unconscious persons, but is not easily executed when consciousness has again been established, because the current of air is then strongly opposed by the voluntary muscles in the region of the glottis, and may in addition be counteracted by those of the thorax. By endeavoring to overcome this resistance serious injury may be inflicted upon the lung tissue, but the conscious subject may overcome these reflexes by remaining passive and by making inspiratory movements in unison with the ingoing blast of air. Tracheotomy obviates

¹ Jour. of the Amer. Med. Assoc., li, 1908, 801.

² A most satisfactory respiration machine has been described by Hoyt, Jour. of Physiol., xxvii, 1901, 48.

³ Henderson, Jour. Am. Med. Assoc., lxvii, 1916, 1.

this difficulty in some measure, but this procedure cannot be resorted to in human beings unless undertaken as a last means to save life.

The manual method of artificial respiration possesses the advantage that it can be applied almost immediately. A delay of more than ten minutes should never result, because it is practically impossible to restore life if this period of time is exceeded. Furthermore, it is to be remembered that the body becomes entirely flaccid in the

FIG. 251.—DEVICE TO ILLUSTRATE THE INFLUENCE OF THE RESPIRATORY MOVEMENTS UPON THE FLOW OF THE BLOOD THROUGH THE PULMONARY BLOOD-VESSELS. (Hering.)

A, bell jar; B, rubber membrane closing it; V, soft rubber pouch to imitate the pulm. blood-vessels; GH, arrangement for forcing water through V under a constant pressure; j, manometer connected with "intrapleural space." On inspiration, produced by moving the rubber membrane downward, the intrapleural pressure is decreased. This gives rise to an aspiration which tends to pull the wall of V outward, facilitating the flow from G to H.

course of ten or fifteen minutes,¹ and that it is then practically impossible to ventilate the lungs by means of pressure with the hands. Respiration not having been restored within this time, it is advisable to resort to the method of inflation, but the apparatus should be placed in the hands of a thoroughly experienced operator.

It is a well-known fact that the arterial blood pressure rises during inspiration and falls during expiration, while the venous pressure rises

¹ Liljestrand, Wollin and Nilsson, *Skand. Archiv für Physiol.*, xxix, 1913, 198.

during the latter and falls during the former period. These changes, which are commonly referred to as the *respiratory variations in blood pressure*, are reversed during inflation. It is easily conceived that the establishment of a positive pressure in the pulmonary passages, corresponding to the normal inspiratory motion, must tend to compress the pulmonary capillaries, thereby producing a stagnation in the venous channels and right side of the heart and a deficiency in its left side and arterial outlets. Just the opposite effect is produced during the period of deflation. Inasmuch as the pressure is now removed from the alveolar walls, the pulmonary blood-bed must be enlarged, allowing a greater quantity of blood to reach the arteries. For this reason, we obtain an inspiratory fall in arterial pressure and an expiratory rise, while, on the venous side, the pressure rises during inflation and falls during deflation.

The methods of artificial respiration previously enumerated are intended to effect either a rhythmic expansion or a rhythmic inflation of the lungs. But it should not be forgotten that these organs may also be retained in a distended condition by the procedure of *constant insufflation*.¹ A long rectangular piece of tubing is inserted through the larynx until its free end comes to lie at the bifurcation of the bronchi. A steady stream of air is then permitted to flow through this tube until the thorax assumes a position of moderate distention. Care must be exercised, however, that the outflow of air along the sides of this tube be not hindered in any way, because an excessive positive pressure gives rise to an immediate fall in arterial pressure dependent upon a compression of the pulmonary capillaries.

CHAPTER XXXIX

THE CHEMISTRY OF RESPIRATION

The Character of the Inspired and Expired Air.—The gaseous metabolism of the tissues consists, on the one hand, in a constant acquisition of oxygen and, on the other, in an evolution of carbon dioxid. This change from one into the other is not accomplished in a direct way, but only with the help of several intermediate reactions which together constitute the process of oxidation. Obviously, the purpose of these reactions is the reduction of the carbon and hydrogen of the food and the liberation of energy in its different forms. The blood and lymph serve as the medium in which this assimilation and dissimilation is effected, while the lungs enable these body

¹ Meltzer, Jour. Am. Med. Assoc., lvii, 1911, 521, also, Zentralbl. für Physiol., xxvi, 1912, 161.

fluids to exchange their gaseous constituents with the surrounding air. Respiration, therefore, consists of two processes, namely, an interchange between the outside air and the blood and an interchange between the latter and the cellular components of the tissues. The former process is known as *external respiration* and the latter, as *internal respiration*.

The fact that the general metabolism of an animal necessitates an intake of oxygen and an outgo of carbon dioxide may readily be gathered from a comparison of the chemical and physical characteristics of inspired and expired air. Concerning the former, it should chiefly be remembered that the inspired air contains more oxygen and less carbon dioxide than the expired. The figures in volume per cent. generally given are the following:

	N	O	CO ₂
Inspired air.....	79.00	20.96	0.04
Expired air.....	79.50	16.02	4.10
		4.94	4.06

Argon, krypton and neon are not included in this table, because they have not been shown to possess a definite function.¹ Besides, it should be remembered that these figures are subject to slight variations, because inasmuch as the composition of the inspiratory air differs somewhat in different localities, the expiratory air must present very similar fluctuations. In addition, the latter exhibits certain minor changes which are caused by periodic variations in the depth of the respiratory movements and intensity of the tissue metabolism. In general, however, it may be said that the air loses during its sojourn in the lungs 4.94 volumes of oxygen and gains 4.34 volumes of carbon dioxide. Its content in nitrogen remains practically the same.

These analyses also show that the volume of oxygen retained is larger than the volume of carbon dioxide given off, which fact seems to indicate that a fractional amount of the former gas is excreted as water. In the second place, the constancy of the nitrogen proves that it possesses no respiratory value other than that it serves as the medium in which the diffusion of the other two gases is enacted. It is to be noted, however, that the expired air generally contains a slight quantity of cellular material which on analysis tends to heighten the percentage amount of nitrogen. In round figures this increase is usually estimated at 0.4 per cent. The expired air may also contain traces of hydrogen and methane which in all probability find their origin in fermentations in the intestines.

Regarding the physical characteristics of the respired air, it is noted that the expired air is warmer than the inspired; but naturally, its actual temperature varies considerably, because the temperature of the inspired air fluctuates with the time of the year and the conditions under which the animal is living. Besides, much depends upon the rapidity

¹ Regnard and Schloessing, *Compt. rend.*, cxxiv, 1897, 302.

and depth of the respiratory movements, the intensity of the metabolism, and other factors. Under ordinary conditions, however, air of 20° C. is warmed to the temperature of the body, or nearly so, while, at lower temperatures, the rise as such may be greater but does not reach 37° C. At 6.3° C., for example, the inspired air is heated to 29.8° C. The greatest heat absorption takes place in the deeper respiratory channels, while the difference in the temperature of the outside air and that in the lower portion of the trachea amounts to only a few degrees centigrade. It is evident, therefore, that this loss of body-heat is effected very largely through the blood of the pulmonary circuit and adjoining venous trunks. This fact is made use of in the open air treatment of respiratory diseases for purposes of lowering the body-temperature. Ordinarily, of course, the respiratory tract of man does not play an important part in heat dissipation, but some animals, and especially those possessing a thick covering of hair, are almost wholly dependent upon this channel for the regulation of their body-temperature.

In consequence of this absorption of heat, the intrapulmonic air increases in volume and becomes nearly saturated with water, but if the necessary corrections are made for the temperature and pressure and if the aqueous vapor is driven off, its volume is slightly less than that of the inspired air ($\frac{1}{250}$ part). This loss is accounted for by the fact that a small portion of the oxygen is not given off as carbon dioxide, but is either united with the sulphur of the proteins or is used in the oxidation of the hydrogen. In the latter case it reappears as water. It will be seen, therefore, that the body loses a certain amount of its heat in the form of bound heat, because a portion of it is set aside for the purpose of warming the air in the pulmonary passages, and a portion for the purpose of converting the water into the gaseous state. This aqueous vapor in the expiratory air is of considerable physiological importance, because at 37° C. its tension amounts to 50 mm. Hg. Assuming, therefore, that dry air is being breathed at the ordinary pressure of 760 mm. Hg, the tension in the deeper recesses of the lungs would amount to only $760 - 50 = 710$ mm. Hg. Thus, the lungs serve not only as a means of regulating the body-temperature, but also as a means of adjusting the water content of the tissues. The expired air is also prone to contain extraneous material, consisting chiefly of fragments of the lining of the pulmonary passage.

The Interchange of the Gases Between the Tidal Air and the Blood.—It has previously been shown that the quantity of air shifted with each respiratory movement is relatively small, amounting on an average to only 500 c.c. For this reason, it must be evident that only the outer respiratory passage is ventilated with each respiration, while the air in the infundibula remains stationary. Consequently, the interchange of the gases between the outside air and the blood, which is commonly designated as "external" respiration, consists in reality of two processes, namely (a) the shifting of the tidal air in

mass and (b) the atomic movement of the constituents of the air in the deeper recesses of the lung. Thus, we have, on the one hand, an alternate inward and outward movement of definite quantities of air and, on the other, an atomic interchange of the gases between the tidal air and the blood directly through the walls of the alveoli and capillaries. The former is a movement of a definite mass of air as a whole and the latter, a progression of the atoms of the gases in accordance with their diffusion pressures and other properties.

The interchange of the gases between the tidal air and the blood has been explained in a physical and in a chemical way. The former explanation, which is commonly accepted to-day, is based upon the ordinary physical laws of the diffusion of gases, while the latter necessitates the assumption that the cells lining the alveoli possess a definite vital activity, leading to a secretion of the gases through this membrane.

The *physical theory*, first of all, recognizes the fact that the gases in the minute air spaces and in the blood are separated from one another by a permeable membrane formed by the lining cells of the alveoli and capillaries. If it is now assumed that the partial pressures of these gases are the same on the two sides of this membrane, an equilibrium must exist which renders the diffusion equal in both directions. But in as much as the body makes constant use of the oxygen and yields in turn carbon dioxid, the region on the inner side of this membrane must give lodgment to relatively much smaller amounts of oxygen and much larger amounts of carbon dioxid than the outer region. Consequently, the partial pressure of the oxygen in the blood must be considerably below that in the alveoli and adjoining larger air passages, while the tension of the carbon dioxid must be greater in the blood. Obviously, therefore, the atoms of oxygen must progress from without to within, while the molecules of carbon dioxid must flow from within to without. Inasmuch as the body does not make use of the nitrogen, this gas remains "stationary," and serves mostly as the medium for the diffusion of the other two gases. It should be remembered, however, that the term "stationary" is only a relative one, because an actual standstill of the atoms of nitrogen, or of any other gas, is not in accord with our modern conception of the behavior of gases. Even when resting, their atoms move about constantly, although they do not advance in large numbers in any one particular direction.

On further inquiry into the conditions prevailing in the intrapulmonic spaces, it is found that the capacity of the bronchial tree is only 140 c.c. and that the air contained therein possesses practically the same composition as the atmospheric. Consequently, the partial pressure of the oxygen in these spaces must amount to 152 mm. Hg and that of the carbon dioxid to practically zero. Keeping these facts firmly in mind, let us see how great a partial pressure these gases exert in the alveoli and in the blood entering the lungs. These values can only be ascertained by a chemical analysis of the air resident

in the alveoli themselves, because as the air from the deeper recesses of the lungs moves outward, it intermingles with that contained in the outer passages, and gives rise to a disproportional relationship of the gases. For this reason, an analysis of ordinary expiratory air cannot yield exact results. It is possible, however, to determine its

FIG. 252.—DIAGRAM TO SHOW THE PRINCIPLE OF THE AEROTONOMETER.

A, the tube containing a known mixture of gases, O, CO₂, N; C, the outside jacket for maintaining a constant body temperature. When stopcock *b* is open the blood trickles down the sides of A and enters into diffusion relations with the contained gases. After equilibrium is reached the stopcock *b* is closed and *a* is opened. By means of the mercury bulb the gases can then be forced out of A into a suitable receiver for analysis. (Howell.)

mean oxygen and carbon dioxid content by collecting the last portions of the air expelled by two forced expirations, one of which follows a normal inspiration and the other, an ordinary expiration (Haldane).

Zuntz and Loewy have calculated the composition of alveolar air by contrasting the capacity of the bronchial tree with that of the alveoli. Thus, if the volume of the expiratory air is reckoned at 500 c.c., 140 c.c. of this amount must be derived from the bronchial tree and 360 c.c. from the deeper recesses of the lung. Furthermore, if the expired air contains 4.38 per cent. of carbon dioxid, the alveolar air must embrace $4.38 \div 1\frac{8}{25}$, or 6 per cent. of this gas. Actual analyses upon human beings have not yielded absolutely constant values, but show variations between 11 and 17 per cent. of an atmosphere for oxygen and between 3.7 and 6.2 per cent. of an atmosphere for carbon dioxid. The average percentage of oxygen, therefore, may be estimated at 14.5, that of carbon dioxid at 5.5, and that of nitrogen at 80. Thus, it will be seen that the oxygen tension in alveolar air amounts to 109 mm. Hg and that of carbon dioxid to 40 mm. Hg. If these figures are now compared with those given previously for the air in the bronchial tree (tidal air), it is evident that the atoms of oxygen must flow from without to within, and the molecules of carbon dioxid from within to without.

In further analysis of this subject matter let us now ascertain whether this relationship also prevails between the alveolar air and the blood. The determination of the tension of the gases in the blood presents several difficulties, because it requires the bringing together of the latter with different gases possessing known tensions, until one is found with which it is in equilibrium. This end is

usually accomplished in a perfectly direct way with the help of an instrument known as an *aërotonometer*. The apparatus, devised by Pflüger, consists of two glass tubes which are placed in a receptacle containing water at 37° C.¹ One of these is filled with a gaseous mixture having a greater and the other with a gaseous mixture having a lesser partial pressure than is expected to be found in the blood under examination. Thus, if it is our intention to determine the tension of the CO₂ in venous blood, which may be estimated at about 4 per cent., one of these tubes is filled with a mixture containing 3 per cent. CO₂, and the other with a mixture containing 5 per cent. CO₂. On permitting the blood to run in a thin

FIG. 253.—A, KROGH'S MICROTONOMETER. B, UPPER PART OF MICROTONOMETER SHOWING CAPILLARY TUBE INTO WHICH THE BUBBLE IS RETURNED FOR MEASUREMENT AND ANALYSIS.

layer down the walls of these tubes, it yields CO₂ to one mixture and abstracts it from the other. The proportion of CO₂ found in the mixtures at the end of the experiment, forms the basis of the calculation of the partial pressure of the CO₂ in the blood, because this value corresponds to the partial pressure which would have to prevail in the tubes in order that the blood be able to traverse them without suffering a change in its CO₂ content.

The *aërotonometer* of Bohr² embodies the principle of the *stromuhr* and permits the blood to reënter the blood-vessel after it has been temporarily diverted into the gas chamber. On this account, these determinations may be continued for a much longer period of time, allowing a thorough equilibrium to be established. Krogh³ uses a small bubble of air which is brought into contact with a correspond-

¹ Modified by Fredericq, *Zentralbl. für Physiol.*, viii, 1894, 34.

² *Skand. Archiv für Physiol.*, ii, 1900, 236.

³ *Ibid.*, xx, 1908, 279.

ingly small quantity of blood until an equilibrium has resulted, which in this case requires a much shorter time than by any of the procedures mentioned previously. The apparatus itself consists of a tonometer and a tubular receptacle for the analysis of the gas bubble. The latter is first played upon by a small jet of blood led in by a narrow cannula, its size being then measured by drawing it into a graduate. The absorption of carbon dioxide and oxygen is carried out in the usual manner by using potash and pyrogallic acid.

Another method frequently employed for the determination of the tension of the gases in the venous blood of the lungs requires the use of a pulmonary catheter,¹

which consists of two tubes, one being situated within the other. The outer tube is somewhat shorter than the inner, and is closed by a rubber balloon which after the insertion of the catheter in the bronchus, is inflated until it completely blocks the respiratory passage. Samples of air are then withdrawn through the inner tube at intervals, until the diffusion of the gases between the alveoli and the blood has continued long enough to establish an equilibrium. Haldane and Smith² have estimated the oxygen tension in the arterial blood in the following manner: The subject is permitted to breathe known quantities of carbon monoxide until the hemoglobin has combined with as much of this gas as it will acquire. The percentage amount of this gas in the hemoglobin is then ascertained in a sample of blood taken either from the finger or from the lobule of the ear. Eventually, when the absorption of carbon monoxide has ceased, its tension in the aerated blood of the lungs will be the same as that in the inspired air. The latter value, as well as the extent to which the hemoglobin has been saturated with carbon monoxide, being known, the tension of the oxygen in the blood leaving the lungs is also known.

FIG. 254.—DIAGRAM ILLUSTRATING THE DIFFUSION OF THE GASES BETWEEN THE TIDAL AIR AND THE BLOOD.

T, trachea; TA, tidal air; B, bronchi; J, infundibulum; C, capillaries; O, oxygen atoms; CO₂, molecules of carbon dioxide.

While the values obtained with these methods show considerable fluctuations, it may safely be concluded that the tension of the gases in the arterial blood closely coincides with that of the corresponding gases in the alveolar air. To be exact, the carbon dioxide of the alveoli is always under a slightly lower pressure than that of the blood, while the oxygen is under a slightly higher pressure. In the latter case, the difference amounts to 1–4 per cent. of an atmosphere; moreover, it has been shown by Krogh to persist even if the composition of the alveolar air is altered artificially.

That is to say, while any change in the tension of the constituents of the alveolar air is immediately followed by a corresponding alteration in the tension of the gases in the blood, the oxygen pressure is always greater in the alveoli than in the blood, whereas the carbon dioxide tension is higher in the blood than in the alveoli.

Much greater differences have been ascertained in the venous

¹ Loewy and Schrötter, *Zeitschr. für exp. Pathol. und Therapie*, i, 1905, 197.

² *Jour. of Physiol.*, xxii, 1897, 231.

blood leaving the heart, in which the tension of the oxygen is 5.3 per cent. = 37.6 mm. Hg and that of carbon dioxide 6 per cent. = 46 mm. Hg. If these values are now contrasted with those previously given for the alveolar air, it is evident that the difference in the tension of the oxygen amounts to $109 - 37$, or 72 mm. Hg, and that of the carbon dioxide to $46 - 40$, or 6 mm. Hg. Consequently, the difference in the tension of the oxygen on the two sides of the limiting membrane is much greater than that of the carbon dioxide; in either case, however, it must be clear that the atoms of oxygen flow into the blood and the molecules of carbon dioxide into the alveoli.

	Oxygen, mm. Hg	Carbon dioxide, mm. Hg
Atmospheric air.....	152	00
Alveolar air.....	109	40
Membrane.....	↓	↑
	—	—
Venous blood.....	37	46

Under normal conditions the lining cells of the alveoli and capillaries offer no hindrance to the passage of these gases, the difference in their partial pressures being sufficient to cause them to move in these directions. At times, however, the orderly flow of the gases may be greatly impaired by infiltrations of the lining cells or by serous material exuded into the alveolar spaces in consequence of inflammatory processes (pneumonia). As may readily be gathered, this difficulty can be overcome in a measure by increasing the driving force behind the atoms of oxygen. With this point in view, pure oxygen is sometimes substituted for the atmospheric air, the intention being to increase the partial pressure of this gas so that at least a part of it will be driven into the system. Obviously, pure oxygen possesses a partial pressure five times greater than that of the oxygen in atmospheric air.

Under normal conditions, however, the diffusion of the gases in the lungs is amply protected, owing to the enormous expanse of the respiratory surface. Upon the basis of 700,000,000 alveoli, possessing an average diameter of 0.2 mm., Zuntz¹ has estimated that the 3000 c.c. of stationary air are in relation with 900,000 sq. cm. or 90 sq. m. of surface.² Thus, it will be seen that each square centimeter of alveolar surface is required to supply only 0.0003 c.c. of carbon dioxide in a minute, the total diffusion of this gas in this period of time being calculated at 300 c.c., namely, at 500 c.c. of tidal air $\times 0.04$ per cent. $\times 15$ respirations. The fact that the diffusion pressure is more than sufficient to furnish the required amount of oxygen, may be gathered

¹ Hermann's Handb. der Physiol., iv, 90.

² Aeby, Bronchialbaum der Säuget. und des Menschen, Leipzig, 1880, 90.

from the following calculation of Loewy.¹ The average thickness of the membrane separating the alveolar air from the blood, amounts to 0.004 mm. In accordance with the diffusion rate of carbon dioxid and nitrous oxid through the lung of a frog, the mammalian lung must yield under a difference of pressure of 35 mm. Hg about 67 c.c. of oxygen for each square centimeter of alveolar wall. The total absorption, therefore, amounts to 6083 c.c., a value much in excess of the actual oxygen requirements of our body in quiet breathing. The latter is only about 250–300 c.c. It must be evident, therefore, that the difference in the partial pressure of the oxygen could safely be much reduced, and that a considerable portion of the total respiratory surface could be rendered functionally useless, before a serious disturbance in the normal supply of this gas would result. In the same way, it has been established that the tension of the carbon dioxid in the blood could be materially decreased without causing a fatal reduction in its flow into the alveoli; in fact, as the speed of diffusion of this gas through a moist membrane is twenty-five times greater than that of oxygen, a difference in pressure of only 0.3 mm. Hg would suffice to yield the 250 c.c. of CO₂ normally expired per minute.

The chemical theory necessitates the assumption that the cells forming the alveolar lining, actively participate in the transfer of the gases. This end is accomplished with the help of inherent processes which are very similar to those occurring in the cells of the secretory glands. Hence, we find here a condition analogous to that existing in the walls of the air-bladder of the fishes. Inasmuch as the contents of this organ consist at times of as much as 85 per cent. of oxygen, the partial pressure of this gas must amount to 90 atmospheres, while that of the oxygen in the surrounding water scarcely exceeds $\frac{1}{5}$ of an atmosphere (Biot). It must be obvious, therefore, that the air-bladder of these animals is filled by a specific secretory activity of the lining cells which is controlled by a special nervous mechanism.²

The first attempt to show that the interchange of the gases in the lungs is not one of simple diffusion was made by Bohr³ in 1890, but these results, indicating that the oxygen tension of the blood frequently exceeds that of the alveolar air, have been seriously criticised by Krogh, as well as by Haldane and Douglass. It seems that certain errors in the manipulation of the aërotonometer and accidental variations in the temperature have rendered these early determinations valueless. In 1907 Bohr endeavored to substantiate his early contentions regarding the secretory activity of the lung by the following experiment: If one lung is permitted to obtain pure air and the other air containing 8.8 per cent. by volume of CO₂, the latter continues to give off CO₂ in spite of the fact that the tension of the CO₂ in the venous blood of the right side of the heart equals that of an atmosphere containing only 5 per cent. of this gas by volume.

This entire subject has recently been reinvestigated by Krogh,⁴ whose micro-aërotonometric tests have shown that the pressure of the CO₂ in the arterial

¹ Handb. der Biochemie, iv, 1908.

² Bohr, Jour. of Physiol., xv, 1893, 494.

³ Skand. Archiv für Physiol., ii, 1890, 231.

⁴ Ibid., xxii, 1910, 274.

capillaries and in the alveolar air is equal, and that the oxygen tension of the latter is always slightly above that of the blood. In addition, attention has been called to the fact that the pulmonary epithelium lacks all the essential characteristics of a secreting membrane. In the mammals, for example, this lining is composed, on the one hand, of small granular cells which are located in the interstitial spaces between the capillaries and, on the other, of extremely thin non-nucleated cells which are situated directly in the capillary wall. Besides, this epithelial covering seems to be entirely lacking in birds, so that the surfaces of the capillaries lie in direct contact with the air. Peculiarly enough, these animals possess a very intense metabolism and must therefore be in a position to interchange the gases with the greatest possible ease. In this connection, attention should also be called to the fact that the function of the pulmonary epithelium cannot be deduced by analogy from that of the limiting membrane of the swim-bladder, because the cells composing the latter are augmented by other cells which form the so-called "red glands" and exhibit true secretory properties. This same statement could not justly be made regarding the lining cells of the alveoli. As another point against the secretory theory might be mentioned the fact that the respiratory activity may be altered at any time by increasing or decreasing the CO_2 content of the inspired air or of that of the blood traversing the respiratory center. Obviously, the assertion might be made that if the lining cells of the alveoli were actually in possession of a secretory power, they should be able to resist outside influences of this kind and should be under the direct control of the nervous system.

Douglass and Haldane¹ have recently attempted to solve this problem in an indirect way by the use of carbon monoxid. It will be remembered that this gas combines with the hemoglobin of the blood to form the more stable monoxid hemoglobin. Thus, if blood is exposed to a mixture of O_2 and CO , a certain portion of each gas eventually unites with the hemoglobin, but inasmuch as the latter possesses a much greater avidity for CO than for O_2 , a much larger amount of CO enters into this combination. Assuming that the same conditions prevail in the body during the inhalation of CO , these authors permitted an individual to breathe a certain quantity of this gas until the blood became fully charged with it. The percentage saturation of the Hb by the CO was then determined. This value may justly be regarded as indicating the O_2 content of the blood, because the amount of this gas which must be inhaled simultaneously with the CO in order to produce the saturation just ascertained, is open to direct calculation. These tests which were supplemented by inhalations of varying quantities of oxygen, showed that the pressure of the oxygen in the arterial blood remains below that of the air in the alveoli until the saturation of the hemoglobin with carbon monoxid surpasses 30 per cent. Beginning at this point, the oxygen tension decreases and is finally reversed. This observation led Haldane to conclude that the epithelial cells of the alveoli play an active part in the interchange of the gases. Thus, it is stated that these lining cells gather the oxygen under a tension of 15 per cent. and force it to the other side of the membrane until its tension in the blood greatly exceeds that in the alveoli.

Several objections may be raised against these experiments which render the conclusions derived from them practically worthless. In the first place, it should be noted that Haldane has employed the colorimetric method of estimating the degree of saturation of the Hb by the CO , a method which has not as yet been proved to be absolutely reliable. Secondly, it cannot rightly be assumed that the avidity of the O_2 and Hb remains the same throughout the course of these experiments, and that the conditions under which these gases unite are the same in vivo as in vitro. For these reasons, as well as others, Haldane has modified his previous contention somewhat, and now seems to believe that the interchange of the gases is accomplished under normal conditions by ordinary diffusion. Under abnormal

¹ Jour. of Physiol., xliv, 1912, 305.

conditions, however, when the oxygen tension in the alveolar air is very low, the lining cells may acquire a secretory power.

The Interchange of the Gases Between the Blood and the Tissues. The Absorption of Gases by Liquids.—If a gas is brought into contact with water, a certain number of its molecules enter the latter and become dissolved, the amount absorbed being dependent upon the nature of the gas, the temperature and the pressure under which it exists. Provided that these factors remain unchanged, an equilibrium is eventually established, during which the water retains a definite quantity of the gas. But this condition of saturation does not signify that the gaseous molecules remain absolutely stationary, because in accordance with the kinetic theory of matter, it is commonly believed that the molecular constituents of any entity are in constant motion. In many cases, they pursue a definite course and collide with one another so that they are deflected from their paths. It should be emphasized, however, that molecular motion does not consist in incessant collisions, because the distances which molecules actually traverse without striking one another are relatively great. Furthermore, it cannot be denied that these mechanical interferences seriously impede the general progress of the molecules. But, while some of them may be momentarily brought to a standstill, others are forced onward with a certain momentum which makes them exceed their average velocity. In the outer layers of the water, large numbers of these molecules strike the walls of the receptacle and rebound, while elsewhere many of them escape into the overlying mass of gas only to reënter the water later on. In the state of saturation just as many molecules leave the water as enter it.

If the preceding experiment is now repeated with a mixture of gases, it will be found that practically the same interchange takes place, the absorption of each constituent being proportional to the pressure exerted by it, *i.e.*, to its partial pressure. Thus, if the pressure of one of the gases is greater in the atmosphere than in the water, it will pass into the water, and *vice versa*. Moreover, it is to be noted that the flow of this particular gas is independent of that of any other of the constituents of this mixture and may be increased or decreased by simply altering its partial pressure in one of these regions.¹

The absorption behaves toward changes in temperature in an inverse manner. Furthermore, inasmuch as these changes are not proportional to one another, it becomes necessary to determine the absorption for every degree of change in temperature. Thus, it has been found that the volume of oxygen absorbed by one volume of water at 0° C. amounts to 0.0489 c.c., that of carbon dioxid to 1.713 c.c., and that of nitrogen to 0.0234 c.c. At 15° C. the volume of these gases absorbed equals 0.0310 c.c., 1.0025 c.c. and 0.0168 c.c., respectively. As a means for comparison we have the so-called coeffi-

¹Law of Henry, Philos. Transact., 1803.

cient of absorption, by which is meant the quantity of a gas physically absorbed or dissolved in 1 c.c. of a liquid at 0°C . and under a pressure of 760 mm. Hg.¹ Essentially the same changes result if a watery solution is brought into relation with a mixture of gases, provided, of course, that no chemical attraction arises between the substances dissolved therein and the gases. It need not surprise us, however, to find that the absorption is less now and gradually decreases as the concentration of the solution is increased.

If a comparison is made between the pressure and the weight of the gas absorbed, *i.e.*, its density or the number of molecules in a certain volume, it will be found that at a constant temperature the weight of the volume absorbed increases and decreases in direct proportion to the increase and decrease in the pressure. To illustrate, the volume of oxygen absorbed by one volume of water at 0°C . and under a pressure of 760 mm. Hg amounts to 0.0489 c.c. If the pressure is now doubled, the volume absorbed remains the same, but its weight is doubled. Quite similarly, a lowering of the pressure below 760 mm. Hg does not affect the volume of the gas absorbed, but solely diminishes its weight (Law of Dalton).

The absorption of the gases by blood or by blood-serum cannot be determined, because oxygen and carbon dioxide form dissociable chemical compounds. In fact, even nitrogen has been said by Bohr to possess certain chemical avidities which do not permit it to conform to the ordinary laws of the diffusion of the gases. This, however, is a debatable question. At all events, the fact that the blood contains the gases just mentioned in physical solution, as well as in a chemically dissociable state, necessitates a brief discussion of the combinations which they may enter.

The Extraction of the Gases from the Blood.—Supposing for the moment that we are dealing with a gas held in ordinary physical solution, the following procedure should be followed. The liquid containing the gas is placed in a cylinder and its upper surface is brought into firm contact with a piston, the weight of which is accurately balanced by a counterweight. If this entire apparatus is now placed into the receiver of an air pump, from which the air may be gradually exhausted, bubbles of gas will escape from the liquid and collect in a thin layer between its surface and that of the piston. At this time, therefore, the piston is being balanced by the pressure of the escaping gas and that existing in the receiver of the air-pump. On increasing the pressure in this compartment, a point will be reached at which the gaseous molecules again begin to enter the liquid. Consequently, at this time the impacts of those molecules which are just leaving the liquid are being counter-balanced, and hence, if the pressure which is required to accomplish this end is noted, we are in possession of a means of

¹Bunsen, *Gasometr. Methoden*, Braunschweig, 1877; Hempel, *Gasanalyt. Methoden*, Braunschweig, 1900, and Berthelot, *Traité pract. de l'analyse des gaz.*, Paris, 1906.

determining the pressure or tension of this gas in the liquid. Thus, it will be seen that a gas can be extracted from a liquid by simply bringing it into relation with an atmosphere in which its partial pressure is slight. The procedure usually followed is to subject the liquid

FIG. 255.—GAS PUMP FOR EXTRACTING THE GASES OF BLOOD. (*Gréhant.*)

M and *F*, the mercury receivers; *P*, the windlass for raising and lowering *M*; *m*, a three-way stopcock protected by a seal of mercury or water; *C*, a cup with mercury over which the receiving eudiometer is placed to collect the gases; *B*, the bulb in which, after a vacuum is made, the blood is introduced by the graduated syringe, *S*. By means of the stopcock *m* the vacuum in *F*, caused by the fall of the mercury, can be placed in communication with *B*. After the gases have diffused over into *F*, *M* is raised, and when the stopcock *m* is properly turned these gases are driven out through *C* into the receiving tube. The operation is repeated until no more gas is given off from *B*. (*Howell.*)

in which the gas is dissolved, to the vacuum of an air-pump or to bring it into relation with some other gas.

The gases of the blood, however, present certain peculiarities because they are not entirely in pure physical solution, but enter loose chemical combinations; in fact, a part of the carbon dioxide forms a stable compound, the dissociation of which necessitates the use of

chemical agents. The usual procedure then is to expose the blood at body-temperature to as perfect a vacuum as can be obtained, but it must have been defibrinated or must have been rendered non-coagulable by the addition of an oxalate or citrate solution.

The Torricellian vacuum was first employed for the extraction of the gases of the blood by Ludwig and Setschenow.¹ Air-pumps of simple construction have been described by Pflüger² and Grehant³ (Fig. 255) and one of greater complexity by Töpler-Hagen. The latter has been modified by Zuntz and Barcroft.⁴ It consists of a Woulfe bottle (*A*) filled with mercury and a long capillary tube which also contains mercury (Fig. 256). Bottle *A* is connected with the water supply

FIG. 256.—BARCROFT'S MODIFICATION OF THE TÖPLER PUMP.

tube by two taps *W*. The vacuum (*B*) is shut off against the sulphuric acid chamber (*E*) for drying the gases by a glassfloat (*Y*). At *F* a condenser is interposed through which a stream of cold water is kept flowing. The blood is led from the cylinder *K* into the receptacle *G* as soon as a vacuum has been established. This end is accomplished by permitting water to flow through the tap *W* into the Woulfe bottle *A*. The mercury is then forced into tube *B*, where its further progress toward *E* is finally made impossible by the raising of the glass valve *Y*. Its only exit now is through *C* into *D*. If the influx of water is now made to cease, and the second tap *W* is opened, the mercury assumes its original position. If the air is at this time prevented from entering at *D*, the valve *Y* drops downward and per-

¹ Ber. der Akad. der Wissensch., Wien, 1859.

² Unters. aus dem physiol. Institut zu Bonn, 1866.

³ Compt. rend., lxxv, 1872.

⁴ Ergebn. der Physiol., vii, 1908, 699.

mits the air from the receptacle *G* and the rest of this connecting tube to enter the chamber *B*. This process is repeated until a high vacuum has finally been attained. A measured quantity of blood is then allowed to flow from the graduated cylinder *K* into the receptacle *G* which is surrounded by warm water to hasten the escape of the gases. The blood boils in this vacuum, but is prevented from boiling away by the condenser. The gases given off by it are then collected over the mercury.

It is also possible to determine the quantity of oxygen or carbon dioxid in a chemical way without the use of the pump. Thus, the CO_2 may be liberated by adding diluted acids to the blood and by collecting it in potassium hydrate.¹ Schultze² has described a simple volumetric method for the estimation of CO_2 which Rieländer has applied to the analysis of the CO_2 in the blood. In recent years Haldane³ has devised an apparatus which has been modified by Fr. Müller.⁴ It is based upon the principle that the oxygen in hemoglobin may be ascertained in a quantitative manner by adding a solution of potassium ferricyanid to laked blood. The apparatus consists of a bottle which is connected with a receptacle containing the solution just mentioned. It also communicates with two burets united below by a connecting piece. The second buret is joined to a bottle which is used as a thermobarometer. A tube leads from the T-cannula to a niveau receptacle filled with slightly acidified water. To the central bottle are attached two glass bulbs separated from one another, as well as from the bottle, by stop-cocks. The upper bulb contains a dilute solution of ammonia and the lower, the blood to be examined.

A perfect constancy of the temperature having been attained, note is made of the level of the water in the burets. If the blood and the solution of ammonia are now permitted to flow into the central bottle, the former will be laked immediately. Under repeated shaking the ferricyanid is then added to the blood after which the level of the water in the burets is observed at intervals. Its maximal fall in the buret nearest the generator indicates the volume of oxygen evolved. In these determinations close attention must also be paid to the temperature as well as to the barometric pressure.

Haldane and Barcroft⁵ have given to this apparatus a more convenient form so that even very small quantities of blood may be examined (Fig. 257). Moreover, Mosso and Marro⁶ have proved that this procedure may be made to include a determination of the carbon dioxid content of the blood. Tartaric acid is employed for the liberation of this gas. The same apparatus may also be employed as a differential indicator of these gases in two different samples of blood.⁷

In the latter case the apparatus consists of two bottles of equal size (Fig. 257) which are connected with a manometer (1.0 mm. bore) filled with oil of cloves of known specific gravity. Into one of these receptacles are then poured 1 c.c. of blood and 2 c.c. of ammonia, made by adding 4 c.c. of strong NH_3 to a liter of water. The blood having been thoroughly laked, the stoppers are anointed with vaselin and their inside compartments filled with 0.2 c.c. of a saturated solution of potassium ferricyanid. The apparatus is then placed in a water bath for about five minutes with both stop-cocks open. At the end of this period the ferricyanid solution is allowed to trickle into the laked blood under repeated shaking of the entire apparatus. It is then replaced in the water bath. The column of the oil of cloves at the side of the blood is now brought to its original level by means of the screw clamp, after which the difference in the levels on the two sides is noted. The volume of the oxygen evolved equals $x = y \left(\frac{v}{p} \right)$ in which y stands for the difference of level

¹ F. Kraus, *Archiv für exp. Path.*, xxvi, 1890.

² *Zeitschr. für die landw. Vers. in Oesterreich*, 1905.

³ *Jour. of Physiol.*, xxii, 1898 and xxv, 1900.

⁴ *Pflüger's Archiv*, ciii, 1904, 541.

⁵ *Jour. of Physiol.*, xxviii, 1902, 232.

⁶ *Rend. della R. Acad. dei Lincei*, xii, 1903.

⁷ Barcroft, *Jour. of Physiol.*, xxxvii, 1908, 12.

and p for the height of the barometer. P may be taken as 10,000 mm., so that the expression $\frac{V}{p}$ may be made to serve as the constant (c) of the apparatus. Then $x = y \times c$.

Having determined the oxygen content of this sample of blood, its carbon dioxid content may be ascertained by the same procedure with the aid of tartaric acid. If it is desired to compare the gas content of two different samples of blood, they are placed in these two adjoining receptacles, 1 c.c. of each under 1.5. c.c. of weak ammonia. They are then immersed in the water bath until the level of the oil remains constant. The blood is then laked in the usual way. If the same quantity of oxyhemoglobin is present in these samples of blood, the level of the oil in the two tubes remains the same; while if unequal amounts are present, the more decidedly venous blood will absorb more oxygen from its bottle than the other. Consequently, the level of the oil must rise on this side, the difference in the

FIG. 257.—BARCROFT'S BLOOD-GAS APPARATUS.

levels indicating the amount of oxygen taken up, and hence, also the content in hemoglobin.

The quantities of oxygen and carbon dioxid vary greatly in different samples of arterial and venous blood. Much depends upon the character of the blood-vessel, or rather, upon the intensity of the metabolism of the tissue supplied by it. Still greater differences are encountered if the blood of different animals is examined. Obviously, these variations pursue a course parallel to the hemoglobin content, as well as to the affinity which this body displays toward oxygen. It is the general opinion that the percentage of oxygen is greater in carnivora than in herbivora and birds, while the percentage of carbon dioxid is smaller. The experiments of Pflüger and others have furnished such values as are included in the following table:

100 C.C. OF ARTERIAL BLOOD CONTAIN:

		O	CO ₂	N
Dog.....	Average	22.6	34.3	1.8
	Maximal	25.4	42.6	3.3
	Minimal	18.7	23.9	1.2
Horse.....	Average	14.0	49.4	
	Maximal	16.6	55.5	
	Minimal	9.2	39.0	
Rabbit.....	Average	13.2	34.0	2.1
	Maximal	14.6	36.5	2.3
	Minimal	10.7	31.3	1.7

A difference of 9 per cent. was frequently encountered, dependent entirely upon the speed of the extraction of the gases; in fact, inasmuch as the oxidations continue for some time after the blood has been removed, a greater yield of carbon dioxide is generally obtained than would be, if these processes could be made to cease immediately. But naturally, this oxidation is restricted to the formed elements of the blood, for the very obvious reason that their metabolism does not cease directly after their escape from the circulation.

The observations of Setschenow upon blood withdrawn directly from the arteries of man have given 21.6 c.c. of oxygen, 40.3 c.c. of carbon dioxide and 1.6 c.c. of nitrogen for each 100 c.c. of blood. Argon is present in very insignificant amounts, its exact value being about 0.04 volume per cent. Traces of hydrogen and carbon monoxide may also be present, the former being derived from the intestinal canal and the latter from the air. Thus, it may be said, in a general way, that 100 c.c. of arterial blood yield about 60 c.c. of a mixture of gases. In the venous blood of the dog the oxygen varied between 5.5 and 16.6 c.c. and the carbon dioxide between 38.8 and 47.5 c.c. If the average values of these determinations, namely 11.9 c.c. and 44.3 c.c. respectively, are now compared with the figures given above, the following averages are obtained for each 100 c.c. of blood at 0° C. and under a pressure of 760 mm. Hg:

Arterial blood.....	20 c.c. O ₂	40 c.c. CO ₂	1-2 c.c. N
Venous blood.....	8-12 c.c. O ₂	46-50 c.c. CO ₂	1-2 c.c. N

The Condition of Oxygen in the Blood.—The plasma of the blood is a watery solution containing 9 per cent. of solids, whereas its formed elements embrace 40 per cent. of solids. At this time, attention should again be called to the fact that the absorption of oxygen by the blood is different from that of oxygen by water, because this gas enters into a chemical combination with the hemoglobin of the red cells. Normal blood, as we have just seen, contains about 20 volume per cent.

of this gas, while 100 c.c. of water under identical conditions are capable of absorbing only 0.7 c.c. (0.7 volume per cent.). This fact, that the oxygen is not simply absorbed by the blood, may also be deduced from the observation that its quantity does not vary directly with its partial pressure in the surrounding medium. It is a well-known fact that blood exposed to the vacuum of an air-pump does not discharge its oxygen until the pressure has been considerably reduced. In most instances a diminution to about half an atmosphere is required before this gas begins to escape. This corresponds to a pressure of oxygen of about 80 mm. Hg. At about 70 mm. Hg the dissociation is intense, and becomes more and more rapid as the pressure declines toward zero. Meanwhile, the blood changes its color from bright red to purple. This behavior of the oxygen clearly proves that it is not held in a simple physical condition, but enters into a dissociable union with some constituent of the blood.

If the blood is now centrifugized, it will be found that the plasma is capable of absorbing only a very small amount of oxygen, while by far the greatest quantity of this gas is held in the corpuscular elements. Only 0.65 volume per cent. are obtainable from the plasma. Another striking difference is the variability of the oxygen content of the plasma in consequence of changes in the tension of this gas in the surrounding medium. If the latter is increased, a greater quantity of oxygen will be absorbed by it, and *vice versa*. Consequently, plasma behaves like water; *i.e.*, it follows the Henry-Dalton law of pressures absolutely. The corpuscular elements, on the other hand, do not show a direct relationship of this kind. To be sure, they also take up a greater amount of oxygen when the partial pressure of this gas is high, but a more copious absorption takes place when its tension is low. As higher degrees of pressure are reached, the absorption becomes less, relatively speaking.

This fact may be illustrated by subjecting defibrinated blood to different tensions of oxygen. At the temperature of the body a pressure of 10 mm. led to an absorption of 6 c.c. of oxygen, while 30 mm. of pressure sufficed for an absorption of more than 16 c.c. Consequently, these low tensions were sufficient to produce a saturation of .80 per cent.; moreover, while higher pressures gave rise to a still greater absorption, the increase obtained with each additional rise in pressure, became gradually less. Thus, with 40 mm. of pressure only 2 c.c. were taken up in addition to those already absorbed, and at 50 mm. only 1 c.c. It has also been ascertained that the degree of saturation of the corpuscles which it is possible to achieve with pure oxygen, namely, with a partial pressure of 760 mm. Hg, is only slightly greater than that obtainable with atmospheric air in which this gas exerts a pressure of only about 150 mm. Whole blood, on the other hand, takes up a somewhat greater amount of oxygen if exposed to it in its pure form, but this oxygen cannot be held by the corpuscles, because they are quite unable to acquire much more than may be chemically united with them. Consequently, this extra amount must be held by them in a physical state and must eventually overflow into the plasma. It need scarcely be mentioned that oxygen thus dissolved in the plasma, obeys the ordinary laws of diffusion, *i.e.*, it escapes from the blood as soon as its partial pressure in the surrounding medium is diminished and long before its chemically combined portion is liberated. These facts indicate

that practically all the oxygen is held by the corpuscles in the form of an unstable chemical compound.

It has been shown that the element which unites with the oxygen, is the blood-pigment or hemoglobin of the red cells. This deduction finds substantiation in the fact that oxygen is bound by crystalline hemoglobin in quite the same way as by whole blood and in perfect agreement with the law of the tension of the gases. Thus, if projected upon an abscissa, the curve of absorption of oxygen by hemoglobin forms a curved line, the convexity of which is turned upward. This result proves that the absorption is greatest at low tensions and least at high tensions, but the employment of hemoglobin, instead of whole blood, introduces several factors which may render a direct comparison of the results practically impossible. In the first place, it is difficult to procure a solution of this pigment which can justly be compared with samples of whole blood, and secondly, it is not always a simple matter to exclude or to control the influence of the carbon dioxid upon the binding power of the hemoglobin. Thirdly, although oxygen and hemoglobin form a dissociable compound, their dissociation tension may be varied by changes in temperature, as well as by the character of the salts present. Human blood corpuscles, for example, are characterized by unusual amounts of potassium, whereas dog's corpuscles contain more sodium. The former salt is notably more efficient in increasing the percentage of saturation of the hemoglobin than the latter. In spite of these difficulties, however, the more recent analyses have given a close quantitative agreement; for example, inasmuch as 1 g. of crystallized hemoglobin takes up about 1.3 c.c. of oxygen, and inasmuch as whole blood absorbs about 20 volume per cent. of this gas, the blood must contain about 15 per cent. of this pigment. The correctness of this value has been established by analytical means; moreover, the absorption of the oxygen may be ascertained directly by determining the binding power of the iron of the blood. Inasmuch as this substance is normally held in measurable quantities only in the hemoglobin, a direct comparison may be made between the absorptive power of this pigment and its content in iron. It seems, therefore, that the hemoglobin is present in amounts sufficient to combine with practically all the oxygen ordinarily contained in the blood.

It has also been found that the oxygen may be displaced from the hemoglobin by equivalent amounts of carbon monoxid and nitrous oxid, and furthermore, may be made to absorb carbon dioxid in greater quantities than can be accounted for by the laws of solution. This fact seems to suggest that the hemoglobin is also capable of entering into a loose chemical combination with this gas, although it does not permit its oxygen to be directly displaced by it. Conditions may arise, therefore, which lead to a simultaneous saturation of the hemoglobin by oxygen and carbon dioxid, thereby altering the oxygen-carrying capacity of this pigment. As has been stated above, it is the

presence of this carbon dioxid which may seriously interfere with the determination of the dissociation curve of hemoglobin and oxygen in whole blood. Its action is similar to that of weak acids, such as lactic acid, because the greater its tension, or the greater the acidity of the blood, the greater is the dissociation of the oxygen. It possesses, therefore, a solvent action which, however, it does not unfold unless the oxygen tension is markedly diminished. To illustrate, under a partial pressure of the oxygen of 150 mm. Hg, the blood remains practically saturated even if its carbon dioxid tension is varied within physiological limits. If the oxygen pressure is now reduced to 20 mm. Hg and the carbon dioxid pressure to 5 mm. Hg, the oxyhemoglobin content of the blood is changed to 67.5 per cent. This value may be further decreased by raising the carbon dioxid tension. This is a matter of great importance to the body, because it facilitates the liberation of oxygen in those parts of the body in which the tension of this gas is low, *i.e.*, in the tissues. By means of this peculiar action of the carbon dioxid, the hemoglobin is relieved of all available oxygen, in fact, of more than it would allow to be transferred to the cells under ordinary conditions of oxygen diffusion.

The Condition of Carbon Dioxid in the Blood.—While the amount of carbon dioxid absorbed by blood, is dependent upon its partial pressure in the surrounding medium, a direct relationship between these factors does not exist. In fact, the volume of this gas actually acquired by a certain quantity of blood, is much greater than the volume which could theoretically be allotted to it upon the basis of its absorption coefficient. It is evident, therefore, that only a part of the carbon dioxid is retained in a physical state, while another part forms a dissociable chemical compound with some constituent of the blood. Conditions, however, are not so simple as they are in the case of oxygen, which gas unites with only one element of the blood, whereas the carbon dioxid is bound to several, *i.e.*, to the plasma as well as to the corpuscles.

If the venous blood of the dog is exposed to the vacuum of an air pump, from 45 to 50 c.c. of carbon dioxid may be extracted from each 100 c.c. of blood. It has also been ascertained with the help of the aërotonometer that this gas is held in the venous current under a pressure of about 40 mm. Hg, or 5–6 per cent. of an atmosphere. This coexistence of a relatively high carbon dioxid content and low degrees of pressure, immediately assumes a greater significance if these values are compared with those obtained with pure solutions of this gas. Thus, if water and carbon dioxid are shaken under a pressure of 760 mm. Hg and at the temperature of the body, about 50 per cent. of the gas will be absorbed. Quite similarly, if blood plasma is treated in this way, it will take up an almost equally large amount of this gas, while whole blood assimilates almost 150 c.c. But naturally, under normal conditions the blood is not exposed to a carbon dioxid pressure of one atmosphere (760 mm. Hg), but only to a pressure of about 40 mm. Hg = $\frac{1}{19}$ of an atmosphere. Hence, all the carbon dioxid, excepting 2.01 c.c. for every 100 c.c. of blood, must be held in chemical combination, and furthermore, if the volume of the corpuscles is reckoned at $\frac{1}{2}$ of the total volume of the blood, these bodies must contain 0.59 c.c. and the plasma 1.42 c.c. of this gas in a

physical condition. Thus, it will be seen that only a very small portion of the carbon dioxide, namely, 5 per cent., behaves in accordance with the Henry-Dalton law.

In endeavoring to locate that portion of the carbon dioxide which is held in a condition of both loose and stable combination, it should first be noted that the serum and plasma contain sodium salts with which this gas could doubtlessly unite. These salts are sodium carbonate and dibasic sodium phosphate. It has been shown, however, that the quantity of available alkali which is combined in the blood in the form of carbonates or phosphates, is not sufficiently large to bind the amount of carbon dioxide normally present. For this reason, it must be concluded that at least a part of this gas is held in a dissociable condition by certain organic substances.

If our attention is now directed to that portion of the carbon dioxide which is united with the alkali of the blood, we are immediately confronted by the difficulty that its quantity cannot be determined with accuracy and that even that part of it which exists as bicarbonate, shows a most peculiar chemical behavior. Thus, defibrinated blood discharges all of its carbon dioxide with greatest ease as soon as it is subjected to the vacuum pump, and even without the addition of an acid to dissociate it from its bases. A bicarbonate solution, on the other hand, possessing the concentration of the blood, liberates scarcely more than half of its loosely bound carbon dioxide. If sodium bicarbonate is then added to whole blood, all of its carbon dioxide can be obtained with the aid of the pump. To these data should also be added the fact that the exposure of plasma or serum to the vacuum does not result in a complete liberation of the carbon dioxide. In order to obtain it in its entirety, it is necessary to add an acid so that this so-called "fixed carbon dioxide" may first be dissociated from its binder. While this point has not been entirely cleared up as yet, it is doubtlessly true that the carbon dioxide is contained chiefly in the plasma where it exists as sodium carbonate or bicarbonate. A certain amount of it is also held in the corpuscles, in all probability in combination with the sodium.

With reference to the organic combinations of carbon dioxide, it should first be stated that the most conspicuous of these is the loose union which this gas is capable of forming with the hemoglobin. At this time, however, reference is had solely to the alkali free portion of this pigment, namely, to its globin molecule. If the hemoglobin content amounts to 15 per cent., and the carbon dioxide tension to 30 mm. Hg, each 100 c.c. of blood contain 8.1 c.c. of this gas in combination with the hemoglobin. In addition, it has previously been shown that 0.59 c.c. are present in the physical state, which makes in all 8.7 c.c. We know, however, that the total absorption of carbon dioxide by the red corpuscles at a tension of 30 mm. Hg amounts to about 14 c.c., and hence, it must be concluded that the remaining 5 c.c. are united with other constituents of these bodies, in all probability with the alkali as bicarbonate and in a small measure also with the lecithin. It has also been shown that the carbon dioxide is capable of forming certain unstable compounds with the proteins of the plasma. As a general summary it might be well to give the table compiled by Loewy¹ which is based upon the fact that under a pressure of 30 mm. Hg each 100 c.c. of arterial blood yield 40 c.c. of carbon dioxide. This total quantity is distributed as follows:

	In plasma, c.c.	In corpuscles, c.c.	In blood, c.c.
Physically absorbed.....	1.2	0.7	1.9
Held as sodium bicarbonate.....	12.0	6.8	18.8
Held in organic combinations.....	11.8	7.5	19.3

¹ Handbuch der Biochemie, iv, 1908.

The Condition of Nitrogen in the Blood.—By far the greatest amount of the nitrogen present in circulating blood, is held in solution and is therefore subject to the law of Henry. The same statement may be made regarding blood kept outside the body, if it is saturated with atmospheric air. It is true, however, that blood always absorbs a larger amount of nitrogen than is taken up by an equal volume of water when subjected to the same conditions. This fact tends to prove that a small portion of this gas is held in combination. Moreover, the presence of this extra amount cannot be dependent upon a special activity of certain tissues for the obvious reason that blood experimented with outside the body, behaves in precisely the same manner. The separate determinations of the nitrogen absorption of the plasma and corpuscles have shown that the nitrogen content of the former is proportional to the tension of this gas, whereas that of the latter is not. Hence, it may be concluded that the corpuscles are the element most directly concerned in this absorption. Besides, it has been proved by Bohr¹ that this union takes place solely in the presence of oxygen and that the factor primarily responsible for it is the hemoglobin. This investigator surmises that the nitrogen is held here in the form of an unstable oxid, the functional significance of which has not been established.

Internal or Tissue Respiration.—The freshly aerated blood traversing the pulmonary veins, left side of the heart and systemic arteries is in a state of almost complete saturation with oxygen which is held here under a pressure of at least 100 mm. Hg. It has been shown above that its saturation amounts to about 90 per cent., and that this degree of saturation can be obtained with an oxygen tension of little more than 30 mm. Hg. Thus, it will be noted that the oxygen-carrying capacity of the blood is amply safeguarded, at least as far as pressure is concerned. This is also shown by the fact that this type of blood may be shaken with atmospheric air at the temperature of the body without absorbing more than about 2 volume per cent. of oxygen in addition to that just stated. Venous blood, on the other hand, requires 8 to 10 volume per cent. of oxygen for its saturation.

The blood traversing the capillaries of the different tissues is brought into diffusion relation with the cells through the intervention of the lymph. It is a well-known fact that the cells acquire oxygen constantly and give off carbon dioxid. It is evident, therefore, that the oxygen tension is higher in the blood than in the tissues, whereas that of the carbon dioxid is higher in the tissues than in the blood. Thus, the physical conditions are such that the oxygen must flow from the blood into the cells, while the carbon dioxid must pass from the cells into the blood, as follows:

¹ Compt. rend., cxxiv, 1897, 414.

	Oxygen, mm. Hg	Carbon dioxid, mm. Hg
Arterial blood.....	100	35
Capillary wall.....	↓	↑
Tissue.....	0	50-70

As far as the exchange of the oxygen is concerned, the conditions existing here are the same as those prevailing when the blood is subjected to the vacuum of an air-pump. The neighboring tissues are always greedy for oxygen, and abstract even the last traces of this gas from the adjoining lymph. The latter in turn must replenish its oxygen content by withdrawing a corresponding amount from the blood. In this way, a descending scale of oxygen tensions is produced, beginning with the red corpuscles and the plasma and lymph and terminating in the interior of the cell. But while the speed of the capillary flow is sufficiently slow to allow these interchanges between the blood and the tissues to be completed with plenty of time to spare, the individual red cells never tarry long enough at these cells to lose their entire store of oxygen. Only if these corpuscles are prevented from recuperating their losses in the lungs can their oxygen store be depleted further until, as occurs in asphyxia, the last traces of this gas have been removed from them. It has been pointed out above¹ that the evolution of the oxygen by the hemoglobin is greatly facilitated by carbon dioxid, this effect being especially marked in conditions of low oxygen tension.

CHAPTER XL

THE SEAT AND NATURE OF THE OXIDATIONS

The Oxidative Power of the Tissues.—It is commonly accepted to-day that the seat of the oxidations is in the tissues and not in the blood, as has been suggested by A. Schmidt² and Pflüger.³ Thus, we are accustomed to compare the body to a steam engine and to speak of the “burning up” of foodstuffs in a manner indicative of the processes taking place during an ordinary combustion. But while it seems to be true that the reductions are confined in their entirety to the cells, the fact must not be lost sight of that they are not always completed by the same group of cells, *i.e.*, while a certain colony of cells may incite

¹ Barcroft, *Respiratory Function of the Blood*, 1914.

² *Arbeiten aus dem physiol. Inst. zu Leipzig*, ii, 1867, 99.

³ *Pflüger's Archiv*, i, 1816, 98.

the oxidation, some other tissue may be called upon to form the final product.

The tissues possess a very pronounced avidity for oxygen. This has been shown in a very convincing manner by Ehrlich. A saturated solution of methylene-blue was injected into the venous bloodstream of an animal. After an interval of ten minutes it was killed and its organs fully exposed to the air. The tissues which exhibited at first their natural color, soon assumed a decidedly blue color. It is evident, therefore, that they are able to decompose the comparatively stable methylene-blue into a colorless product, which on exposure to the air is again oxidized into methylene-blue. It has also been noted that hemoglobin-like bodies are present in the cytoplasm of the cells of the worms, presumably for the purpose of effecting respiratory interchanges. In addition, Lillie¹ has found that the colored products of the oxidations, such as may be obtained in the course of indophenol and similar reactions, accumulate chiefly in the vicinity of the nuclei. Some light is also thrown upon this question by the fact that the tissues contain large quantities of carbon dioxid and that this gas is present in considerable amounts in the lymph occupying the peripheral radicles of the lymphatic system. It might also be mentioned that a frog may be kept alive even after its blood has been replaced by physiological salt solution, by simply placing the animal in an atmosphere of pure oxygen. Inasmuch as the consumption of oxygen and the production of carbon dioxid are had in this instance even in the absence of the blood, these processes must actually be completed in the tissues. The same result may be obtained with excised muscles, in which case the production of carbon dioxid follows a course parallel to the activity and general condition of this tissue.

In whatever form the energy of the body may be liberated, its source lies in cellular combustions which in turn necessitate respiratory interchanges. The nature of these microchemical and microphysical processes is not clearly understood, nor has the chemist been able to form a concise picture regarding the changes that occur during one of the simplest possible combustions. On this account, it is quite impossible to describe these processes in anything more than a very general way. When the blood enters the tissues, it delivers not only a definite amount of oxygen, but also certain amounts of nutritive material in the form of proteins or amino acids, fats and sugars. These substances are acted upon within the boundaries of the cells. Consequently, the processes of life consist in an uninterrupted change in energy which presents itself as a conversion of latent energy into work, heat and electricity. It is to be noted, however, that animals are not capable of sustaining themselves unless fully formed organic substances are placed at their disposal, and hence, the amount of energy which they produce, is absolutely dependent upon their power of reducing these organic molecules. Plants, on the other hand, are able to

¹ Am. Jour. of Physiol., vi, 1902, 15.

form these complex substances from inorganic material by permitting carbon dioxide and water to act in the presence of sunlight. Obviously, therefore, animal life depends upon the products of the higher plants, for the reason that the latter contain energy-rich organic material.

While these general facts are incontestable, much uncertainty still prevails regarding the nature of these reducing processes. In its widest sense, the term oxidation is applied to any chemical reaction which results in an increase of the positive or a decrease of the negative valencies of a compound. Whether or no oxygen or some other agent is the cause of the reduction is not of deciding value. Thus, the evolution of iodine during the action of ferric chloride upon potassium iodide is essentially an oxidation, as may be gathered from the following formula:

This process has resulted in the passage of a positive charge of electricity from the ferric atom to the iodine atom, or the transfer of a negative charge of electricity from the iodine ion to the ferric ion. It will be seen that a substance which freely yields a negative charge is a very active reducing agent, while a substance which readily liberates a positive charge is a powerful oxidizing agent. Upon this basis, oxygen may be said to act as an oxidizing body, because it possesses the power of removing a negative charge from other substances and of attaching itself to them as an oxygen ion, or as electronegative oxygen.¹

At this time, however, we are chiefly concerned with those processes which are consummated in the living tissues with the aid of oxygen. These reductions belong to the class of the slow reactions, and are not simple combustions, because the oxidations are generally initiated by reductions participated in by various ferments, *i.e.*, the complex molecules are first simplified by catalytic agents before they are actually oxidized. It should also be remembered that these oxidations may result in many cases without any apparent stimulus, while in others the substances must first be activated by some outside agent. Thus, metallic sodium, phosphorus and certain organic bodies bind free oxygen even at ordinary temperatures, while the rare metals, wood and coal must first be exposed to a high temperature. The former process takes place slowly and the latter with considerable speed. Quite similarly, foodstuffs possess no tendency to take up atmospheric oxygen under ordinary conditions but may be made to unite with this gas by heating them. Their combustion may be incited immediately by exposing them to the temperature of a flame, while at the temperature of the body, the upper limit of which is near 40° C., their oxidation is slow and gives rise to intermediary substances. For this reason, they are classified as dysoxidizable substances.

¹ Barcroft, *Ergebn. der Physiol.*, viii, 1908, and Winterstein, *Dissertation*, Jena, 1906.

In the second place, it should be remembered that a substance may be very closely allied to one of the known oxidizable bodies, and still fail completely in being oxidized by the tissues. Thus, it has been found that only four of the sixteen sugars, possessing the formula $C_6H_{12}O_6$, namely, glucose, fructose, galactose and mannose, are acted upon by the cells, while the others cannot be utilized. In the third place, a tissue may lose its power of reducing certain foodstuffs completely, a condition met with in diabetes mellitus. Consequently, the cell must possess a certain chemico-physical constitution which becomes completely disarranged in the course of certain diseases with the result that formerly assimilable substances are rendered non-assimilable. It is evident, therefore, that the general arrangement of the intracellular material constitutes the principal factor in the determination of the manner in which the dysoxidizable foodstuffs combine with the oxygen. On this account, there is imparted to the oxidations a definite specificity and a limit is set to them in conformity with the requirements of the different tissues. Consequently, the magnitude of the oxidation is regulated by the tissue itself and not by the amount of oxygen actually available. Thus, inhalations of pure oxygen cannot augment the oxidations, because the tissues are already acting at their fullest capacity. The oxygen which is required for these processes may be furnished either in a free or bound state. In the latter case, it is in combination with some of the nutritive substances. As bound oxygen must also be regarded the oxygen of water which, on account of its wide distribution, must play a most important part in biological oxidations. The latter are commonly designated as hydrolytic oxidations.

As slow combustions are the rule in living matter, the energy which is required to instigate these processes must be furnished by the substances to be oxidized. The latter, therefore, must possess the power of activating the molecular oxygen, and hence, the real purpose of respiration is to allow the mechanism of the activation of oxygen to be set in motion. Unfortunately, however, the nature of this process is not clearly understood, although several theories have been formulated to serve as possible explanations.¹

The theories regarding the activation of oxygen may be divided into two groups, namely: those which assume that the oxygen is first of all split into an active modification and those which hold that the molecules of oxygen are used in their complete form. Among the former may be mentioned:

1. The ozone-autozone theory of Schönbein and Clausius which assumes that the inert oxygen appears in the form of two different and active modifications.
2. The ionization theory of van't Hoff which holds that the modifications of the oxygen are not chemically different but only carry different electrical charges.

¹ A more detailed account will be found in Oppenheimer's *Handbuch der Biochemie*, Jena, 1913, or in Mathews, *Physiol. Chemistry*, New York, 1915. Also see Engler and Weissberg, *Krit. Studien über die Vorg. der Autoxydation*, Braunschweig, 1904.

3. The theory of Hoppe-Seyler denies these peculiarities of the oxygen-fraction and explains this reaction upon the basis of reductions in which nascent hydrogen plays a part. It is said that reducing substances are formed by the hydrolytic splitting of the foodstuffs in consequence of ferment activity. The atomic hydrogen acting upon the oxygen, forms water during which process some atomic oxygen is left over which is used to oxidize the split products of the fermentation.

Traube,¹ on the other hand, advocates the view that the molecule of oxygen acts in its entirety. He assumes, however, that the oxidizable substances are not acted upon by free oxygen but only by the bound oxygen of the water. Thus, it is stated that the molecule of water is first split into its components, oxygen and hydrogen, and that the former is combined with the oxidizable body and the latter with one whole molecule of oxygen to form hydroperoxid. This theory, however, does not give satisfactory answer to the question of why the oxidizable substance prefers bound oxygen to free oxygen and why the latter selects the hydrogen of the molecule of water and not the oxidizable body. But, this theory possesses the advantage of being more truly chemical, because it minimizes the atomic action of oxygen and calls attention to the primary formation of hydroperoxid. Much greater emphasis has been placed upon this process by Engler² and Bach³ who believe that the oxygen-molecule $O = O$ is incompletely split by the free energy of the oxidizable one, so that $-O-O-$ groups arise which combine with the former under the formation of primary peroxid. Inasmuch as one-half of the oxygen is contained in these peroxids in a loose and active state, it can be transferred without difficulty to other oxidizable substances.

Hydrolytic oxidations include first of all those processes which are accomplished with the help of the peroxid-oxygen and secondly, those which are carried on at the expense of the hydroxyls of water. But, the separation of the latter necessitates the presence in the substance of a relatively large amount of energy consisting in an affinity for the hydroxyls. Substances of this kind are few in number and hence, it generally happens that two substances take part in the hydrolysis, one of which attracts the hydroxyl and the other the hydrogen. As an example of this type of oxidation, Bach⁴ cites the splitting of water by hypophoric acid or its salts in the presence of metallic palladium.

While the peroxid theory of combustion as such enables us to explain many phenomena of life which would otherwise remain hidden to us, several facts have been added to it in more recent years which render it even more serviceable. Thus, it has been established that the oxidations do not actually affect the substance of the cells and cause its destruction, but merely take place in its presence under the influence of specialized ferments. The latter, of course, are a product of the cells and hence, we are dealing in this case with a chemical process during which the organized cytoplasm does not suffer. As an analogous reaction might be mentioned the conversion of sugar into alcohol and carbon dioxid by the living yeast cell.

The biological oxidations are slow combustions, and as such must be subject to the influence of catalytic agents. In the sense of Ostwald, therefore, these processes are catalyses, *i.e.*, true reactions, instigated

¹ Chem. Berichte, xv, 1882, 659; xviii, 1885, 1877, and xviii, 1885, 1890.

² Ibid., xxx, 1897, 1669.

³ Compt. rend., cxxiv, 1897, 951.

⁴ Chem. Berichte, xlii, 1909, 4463.

by an outside factor which does not enter into the formation of the end-product. This view is strengthened considerably by the fact that living substance contains three types of catalyzing agents in the form of ferments, namely, oxidases, peroxidases and perhydridases. Since these ferments possess a special function in so far as they complete the process of respiration, they may be classified as *respiratory ferments*. As such they are comparable to the class of the "digestive" ferments. Thus, a fat-splitting enzyme (lipase) and protein-splitting enzymes (proteases) have been isolated from many tissues, and ferments have also been found which act upon starch (amylase) sugar (diastase) and glycogen (glycogenase). The fact that such catalyzing agents exist in tissues is well illustrated by the phenomenon of autolysis or self-digestion. If a tissue is removed from the body under aseptic conditions and is kept warm and moist, it will finally be digested. The same end-products are then formed as may be obtained by boiling this tissue with acids.

In general, therefore, it may be said that the reductions in living matter occur either in the presence or in the absence of free or bound oxygen. At this time, however, we are chiefly concerned with those of the first type, namely, with the respiratory reductions. In accordance with the foregoing discussion it must now be evident that the purpose of respiration is the burning up of the simplest constituents of the body. This combustion is made possible by the respiratory ferments which are produced by the cell and exert their action as soon as the foodstuffs have been sufficiently simplified by the ferments of the digestive type. The former, therefore, are organic catalyzing agents which may be arranged in the following sequence:

1. Oxidases, produce their action with the help of free oxygen.
2. Peroxidases, hasten the formation and action of the peroxids, *i.e.*, of those easily oxidizable substances which take up molecular oxygen to form peroxids. These organic peroxids produce the same effects as hydrogen peroxid, from which atomic or active oxygen is removed as follows: $\text{H}_2\text{O}_2 = \text{H}_2\text{O} + \text{O}$. At the present time, however, no evidence is at hand to prove that hydrogen peroxid is actually formed in the tissues, although it seems that it is produced in the green leaves of plants in the course of their assimilation of carbon.
3. Perhydridase, hastens the reduction of the water-molecule by aldehyds. This ferment, therefore, regulates the hydrolytic cleavage and liberates the oxygen of the water.
4. Catalase, changes hydroperoxid into molecular oxygen and water. This substance is very prone to be formed in the course of these processes either in a direct way or from peroxids. It would eventually destroy life. Consequently, this ferment really serves as a protection to the cell, because it causes its removal.

The power of the cell to regulate the intensity of its oxidations is dependent upon its faculty of producing ferments of the preceding types. Secondly, it is also evident that the action of the cells is specific, because several of these ferments affect the oxidation of only particular substances. For this reason, special names have been applied to them, such as xanthinoxidase, tyrosinase, etc. The former,

for example, accomplishes the oxidation of hypoxanthin and xanthin to uric acid, while the latter regulates the oxidation of tyrosin. In this connection, mention should also be made of the fact that oxidizing ferments, or oxidases, are widely distributed through the vegetable tissues. Thus, guaiaconic acid may be oxidized by the latter in the presence of atmospheric oxygen, and peroxid of hydrogen is not needed by them to color guaiacum blue. Quite similarly, many fungi contain a ferment known as tyrosinase which, when added to solutions of tyrosin in the presence of air, oxidizes the tyrosin into a brown pigment. The brown discolorations upon the cut surfaces of apples and potatoes are attributed to the oxidation of a chromogen by the oxygen of the air under the influence of an oxidase.

CHAPTER XLI

THE RESPIRATORY INTERCHANGE UNDER DIFFERENT CONDITIONS

The Respiratory Quotient.—The quantity of air respired in a day amounts to about 11,000 liters. In a man weighing 70 kg., this amount of air is brought into relation with a diffusion surface measuring about 90 sq. m., so that 1 kg. of substance possesses a breathing surface of 1.28 sq. m. A person of this weight produces under ordinary conditions about 250 c.c. of carbon dioxid for each kilogram of weight in an hour, or 428 liters in the course of a day. During absolute rest or sleep the CO₂ production is of course greatly diminished, amounting to only 160 c.c. in an hour. Excessive muscular exercise, on the other hand, increases it considerably, to possibly 1200 c.c. in an hour. Furthermore, it may justly be assumed that the production of 85 c.c. of carbon dioxid necessitates the absorption of 100 c.c. of oxygen. The relation between the quantities of O absorbed and CO₂ liberated during a given period of time is designated as the respiratory quotient.¹ Since the air during its sojourn in the lungs loses 4.78 volume per cent. of O and acquires 4.34 volume per cent. of CO₂, the respiratory quotient is: $\frac{\text{CO}_2 \text{ 4.34}}{\text{O 4.78}} = 0.901$. This value, however, is subject to fluctuations, because the amount of oxygen required to oxidize the carbon seldom remains the same for long periods of time. It is under the constant influence of such factors as: species, diet, age, temperature, muscular activity and the composition of the inspired air.

The respiratory quotient of warm-blooded animals is larger (0.7 to 1.0) than that of cold-blooded animals (0.65 to 0.75), because the latter consume less oxygen for each kilo of body-weight than the former. The frog, for example, possesses

¹ Zuntz, Hermann's Handb. der Physiol., iv, 90.

an oxygen requirement of only 0.07 per kilo of weight, which is from 6 to 18 times smaller than that of different species of warm-blooded animals. When considered in a relative way, it also holds true that the smaller animals display a more intense respiratory interchange than the larger. This fact may readily be deduced from the following compilation, containing the oxygen consumption for each kilo of weight: in the horse 0.437, calf 0.48, sheep 0.499, ox 0.55, rabbit 0.92, and cat 1.00. This rule may also be applied to animals of the same species, because the body-surface of the smaller ones is more extensive in relation to their body-weight than that of the larger. This implies that the loss of heat is proportionately much greater in the smaller animals and must be compensated for by an increase in their metabolism. This in turn necessitates a greater consumption of O and production of CO₂. Thus, while an animal weighing 2.1 kg. gives off 1.02 g. of CO₂ for each kilogram of weight in an hour, one weighing 3.1 kg. yields only 1.96 g. in all.

The respiratory quotient is higher in herbivora (0.9 to 1.0) than in carnivora (0.7 to 0.8) or omnivora (0.8 to 0.9). These differences find their cause in the character of the *food*, because the formation of CO₂ from carbohydrates, upon which herbivora feed, requires the use of all the O for the reduction of the molecules, while the H has already acquired an amount of O sufficient to satisfy it. During the disintegration of the fats and proteids, on the other hand, a portion of the O is employed for the oxidation of the H to form H₂O. For this reason, the quotient is lowered by a diet rich in proteid material, and heightened by vegetable foods. It must approximate unity (1.0) as soon as a sufficient amount of carbohydrates has been ingested. For example, since 6 molecules of O oxidize 1 molecule of grape sugar ($C_6H_{12}O_6 = 6CO_2 + 6H_2O$), the quotient must be $\frac{6CO_2}{6O_2} = 1$. In the case of the fats which require a much greater number of molecules of O, the quotient must, of course, become smaller. Olein, for example, needs 80 molecules of O to reduce its molecules, as follows:

$C_3H_5(C_{18}H_{33}O_2)_3 = 57CO_2 + 52H_2O$; hence, the quotient must be $\frac{57CO_2}{80O_2} = 0.712$.

Inasmuch as the proteins vary considerably in their composition and are not oxidized in their entirety in the body, their quotient can only be arrived at by calculation. Thus, it has been estimated that this value in the case of albumin varies between 0.75 and 0.81, in accordance with the degree of disintegration of the substance. During periods of starvation the quotient remains below normal, because all the available carbohydrates have been utilized and the body subsists on its own proteids and fats. The production of CO₂ then falls off at a greater rate than the consumption of O. In diabetic patients, whose consumption of carbohydrates is at a minimum, the respiratory quotient is very low, namely, 0.6 to 0.7. Hence, it will be seen that the respiratory quotient at any given moment is dependent upon the nature of the substances undergoing oxidation. Atwater has furnished the following table:

Starch.....	1.0
Cane sugar.....	1.0
Glucose.....	1.0
Animal fat.....	0.711
Protein.....	0.809

In *hibernating animals* the quotient becomes very small (0.25), because the output of CO₂ and the consumption of O are enormously reduced, but the former in a greater measure than the latter. The CO₂ output is also diminished during *sleep* and more so than the intake of O. The quotient, therefore, becomes smaller than normal. Brief *muscular exercise*, on the other hand, increases it immediately, because a considerable quantity of carbon dioxide is then washed out of the active tissues. During longer periods of muscular activity the quotient remains practically the same, in spite of the fact that greater amounts of CO₂ and O are worked

over. On a mixed diet, however, their relationship remains practically unaltered. The ingestion of different foodstuffs changes matters considerably. Thus, the quotient rises to 1, if the muscular work is performed exclusively at the expense of the carbohydrate material. This is rarely the case, although muscular work depends chiefly upon the carbohydrates, because these bodies are more immediately available and may also be slowly replenished from the proteins. The fats may also be drawn upon, but since there is no evidence at hand to show that these substances are first converted into carbohydrates, it must be concluded that the muscles are capable of utilizing them as such. Obviously, therefore, the respiratory quotient serves as a reliable index of the oxidations only if the determinations establishing its value have been extended over a long period of time. Short experiments may lead to absolutely erroneous results on account of the occurrence of accidental variations, such as occasional muscular contractions and voluntary changes in the depth of the respiratory movements.¹ Even the mere ingestion of food may increase the gaseous exchange, because it augments the mechanical and secretory activities of the alimentary canal.² None of these influences possess a permanent metabolic value.

Sex and age influence the quotient through the general metabolism. In males the average CO₂ output is greater than in females, but this general difference between the sexes is not in evidence if persons of the same body-weight are compared. The influence of age manifests itself by the low value of the quotient in children as compared with that of adults. Not only is the gaseous interchange in proportion to the weight greater in the former, but more O is being absorbed by them in comparison with the CO₂ given off. Obviously, therefore, the child possesses a more intense metabolism, presumably on account of the fact that its surface in proportion to its weight is larger than that of the adult, thereby entailing a greater loss of heat. Aside from this factor, age also influences the respiratory interchange because the tissues gradually become less active. For the same reason, the respiratory activity is greater in the robust than in the weak or sick.

Increases in the *external temperature* tend to heighten the gaseous interchange and hence, to increase the quotient. In cold-blooded animals, in particular, the CO₂ output decreases as the temperature of the medium falls and increases as the latter rises. In warm-blooded animals, on the other hand, cold within physiological limits has a tendency to stimulate the consumption of O as well as the production of CO₂. Involuntary muscular tremors (shivering) increase the respiratory activity, the oxygen intake as well as the CO₂ output becoming greater.³ When the body temperature rises, as in fever, the respiratory quotient remains at first practically the same, although the volumes of O absorbed and CO₂ produced are increased.

The *rate and depth* of the respiratory movements do not appreciably change the relationship of the O and CO₂, although, to begin with, the more ample ventilation of the lungs tends to heighten the CO₂ output. If the respiratory amplitude remains the same while its rate is increased, the volume of air respired, as well as the absolute quantity of CO₂ discharged, is increased, but the amount of CO₂ in comparison with the total volume of air becomes less. Very similar results are obtained if the depth of respiration is increased while the frequency is permitted to remain the same. Slow and deep respirations, of course, give rise to a greater discharge of CO₂.

The *composition of the air* may be changed considerably before the gaseous interchange is markedly altered, because a variation in the partial pressure of the two principal gases is generally compensated for by changes in the activity of the body as well as in the gas content of the blood. This compensation, however, has its limits, so that any extraordinary alteration in the partial pressures of the gases

¹ Benedict and Cathcart, *Musc. work, etc.*, Carnegie Institution of Washington, 1913.

² Zuntz and Mehring, *Pflüger's Archiv*, xxxii, 1883. 173.

³ Speck, *Deutsch. Arch. für klin. Med.*, xxxiii, 1889, 375.

of the atmospheric air must finally lead to a serious disturbance of the normal metabolism. The conditions to be dealt with at this time are a decreased and increased supply of oxygen and an increased supply of carbon dioxide. In all these cases we are concerned with changes in the volume per cent. of the gases.

A diminution in the partial pressure of the oxygen of the air must necessarily induce a similar change in the pressure of this gas in the alveoli. But inasmuch as the intensity of the pulmonary ventilation and the magnitude of the oxygen consumption vary almost from moment to moment, a direct relationship cannot exist between these factors, and hence, it is more correct to speak of the tension of this gas in the alveoli than of that in the surrounding air. While the lower limit of the former, which may be endured without danger to life, differs somewhat in different persons, it may be adjudged at 30–35 mm. Hg. This value, of course, holds true only under a normal atmospheric pressure and corresponds to an oxygen content of the alveolar air of 4.5 per cent. Consequently, provided that 500 c.c. of air are respired 17 times in a minute, an altitude of 5000 m. may be attained before the oxygen tension in the alveoli reaches this low level.¹ Any difficulty arising therefrom, may be remedied immediately by increasing the amplitude of the respiratory movements. This change augments the alveolar tension and enables the individual safely to ascend even to somewhat higher altitudes if he reduces his muscular activity to a minimum. Paul Bert² places the lower limit of the oxygen pressure of the outside air at 50 mm. Hg, which corresponds to an oxygen content of 6 to 7 per cent. At this time, the total atmospheric pressure amounts to 250 mm. Hg. An animal which is exposed to still lower tensions develops symptoms of dyspnea and convulsions which generally terminate fatally. An oxygen content of 12 per cent. is usually endured without changing the quality of the respiratory movements, although the deficiency in oxygen may be quite apparent from the bluish color of the face.

In explaining this phenomenon it is commonly believed that an alveolar tension of the oxygen of about 30 mm. Hg causes the oxyhemoglobin to be dissociated so rapidly that the blood is no longer in a position to aerate the tissues properly. Hence, we are dealing here with a real deficiency in the oxygen supply which is commonly designated as anoxemia. This explanation may also be expressed as follows: We know that for physical reasons the system cannot absorb the oxygen under a lower tension than the one just given. Consequently, the 350 c.c. of oxygen which each kilogram of substance requires in an hour can only be obtained with a differential pressure of 29 mm. Hg or more. If the pressure falls below this value, the driving force behind the atoms of oxygen becomes so slight that they cannot traverse the alveolar lining to enter the blood.

An increase in the partial pressure of the oxygen in the alveoli can be attained either by the inhalation of a mixture of gases which is rich in oxygen, or by the inhalation of pure oxygen under atmospheric pressure. But even if this gas is supplied in a pure form, so that its pressure is increased five times, namely, from 152 mm. to 760 mm. Hg, no considerable variation in the consumption of oxygen and the output of carbon dioxide results; provided, of course, that the experiment is not continued for an unusually long time. This fact tends to show that the oxidations in our tissues cannot be affected in a favorable manner by this means so long as physiological conditions prevail. It also proves that the atmospheric air contains an amount of oxygen which is more than sufficient to satisfy our needs. Any variation in our requirements is immediately adjusted by changing the respiratory rate and amplitude. But while ordinarily no advantage can be derived from breathing pure oxygen, this procedure may prove beneficial in those diseases which are associated with pulmonary infiltrations and a poor aeration of the tissues. In accordance with the foregoing discussion, it must be clear that all we can hope to accomplish by this means is to increase the driving force behind the atoms of oxygen,

¹ Loewy, *Respiration und Zirkulation bei Änder. des Sauerstoffgehalts der Luft*, Berlin, 1895.

² La pression barométrique, Paris, 1878.

and to impart to them a greater penetrating power. In this way, at least a partial aeration of the tissues may be retained for some time after the respiratory movements have become inadequate, or after the alveolar spaces have become blocked by exudated material (pneumonia). Especially beneficial results are obtained in certain heart diseases, in which the supply of oxygen has become insufficient on account of the impairment of the circulation. The oxygen seems to exert a stimulating influence upon the musculature of the heart in consequence of which its contractions become more forceful.

If the oxygen is inhaled under a pressure of from 3 to 4 atmospheres, it acts as a poison, death resulting in the course of a short time from respiratory depression, loss of heat and a general intoxication. The same effect may be produced by the continued inhalation of ordinary air under a pressure of from 15 to 20 atmospheres. It has also been shown that the development of the eggs of insects is greatly retarded if exposed to an oxygen pressure of less than one atmosphere. Fish are killed when the oxygen content of the water is raised so that 100 c.c. contain more than 10 volumes of dissolved oxygen. Quite similarly, it was found by Smith¹ that mice which had been exposed for several hours to an oxygen pressure of 2 atmospheres acquired a subnormal content in oxygen. These animals then exhib-

FIG. 258.—EFFECT OF CO₂ ON RESPIRATORY MOVEMENTS OF RABBIT. (Scott.)

During the first period indicated on the signal line the animal breathed 9.6 per cent. CO₂ in air, and during the second period 10 per cent. CO₂ with 33 per cent. oxygen. Time tracing = 2 seconds.

ited inflammatory changes of the lining cells of the alveoli, similar to those observed in pneumonia. A longer exposure to this gas proved fatal in a few days. Facts such as these unmistakably prove that the administration of oxygen is not at all without danger.

A slight increase in the partial pressure of the carbon dioxide (to 5 per cent.) is reacted against as a rule by an increase in the respiratory rate and amplitude (hyperpnea), but the intensity of the oxidations is not materially changed.² In those cases in which a greater output of carbon dioxide has actually been observed, the change seems to be due to the greater activity of the muscles of respiration. If the carbon dioxide in the inspired air is increased to 8 or 10 per cent., dyspnea results; the output of carbon dioxide is diminished and later on also the intake of oxygen. A further increase in the partial pressure of this gas to 15 per cent. leads to an augmentation of these conditions until, at concentrations of from 30 to 40 per cent., a respiratory depression sets in which is soon followed by the death of the animal. At first, therefore, the tendency is to increase the ventilation in the alveoli by hyper efforts at respiration so as to maintain the tension of this gas in the blood. This change is accompanied by a rise in blood pressure which is caused in part by a greater cardiac output and in part by a constriction of the blood-vessels. Later on, however, as the tension of the carbon dioxide is increased to 15 per cent., the

¹ Jour. of Physiol., xxii, 1898, 307.

² Speck, Menschl. Atmung., Leipzig, 1892.

dyspnea gradually becomes more evident until it eventually gives way to a respiratory and circulatory depression similar to that observed in deep narcosis (Fig. 259).

Changes in Barometric Pressure.—It is also feasible to change the pressures of the gases by altering the barometric pressure. This can be done either by compressing the air surrounding us, or by changing our altitude. Thus, a deficiency in oxygen may be produced either by placing an animal into a chamber in which the oxygen tension is low or by bringing it to a higher altitude. As is indicated in the succeeding table, the pressure decreases the more, the higher the altitude.

FIG. 259.—RECORD OF THE CAROTID BLOOD-PRESSURE DURING DYSPNEA (DOG).
At L the tracheal tube was held shut until the blood-pressure began to drop.

Elevation above sea level, m.	Barometric pressure, mm. Hg	Per cent. of an atmosphere
0	760	100
1000	670	88
2000	593	78
3000	524	69
4000	463	61
5000	410	54
6000	357	47
7000	320	42

Sojourns in rarefied air give rise to a complex of symptoms which are grouped under the term of *mountain sickness*. A person affected in this way suffers from headache, nausea, vertigo, hemorrhages and a general mental and bodily apathy. It is true, however, that the altitude at which these symptoms appear is not the same for all individuals, because a process of adaptation is frequently brought into play which allows the continuance of normal function even at higher

altitudes. Most generally, however, an elevation of about 4000 m. suffices to produce definite discomforts and especially if the consumption of oxygen has been markedly increased on account of the muscular exertions incurred during climbing. At a height of 5000 m., at which the pressure of the air is reduced to about one-half and the oxygen tension to about 11 per cent. of an atmosphere, scarcely anybody escapes the sensations of fatigue and respiratory oppression. Neither is it possible to obviate these difficulties by ascending to these heights in a balloon, because even in the absence of all unnecessary muscular activity, the body is in need of more oxygen owing to an increased action of the heart and a compensatory augmentation of the cellular oxidations. More favorable conditions, however, may be established during balloon ascensions, and hence, somewhat higher altitudes may be attained in this way. Altitudes of 7000–8000 m. and over may be reached by resorting to inhalations of pure oxygen, but even this artificial means does not afford an absolute protection against the development of dangerous conditions. This is shown by the experiences which Tissandier¹ had while ascending in a balloon to a height of 8600 m. At an altitude of 7500 m. he and his two companions became so weak that they could not make effective use of the oxygen bags. All three persons finally lost consciousness but without having previously experienced a decided dyspnea. Tissandier was the only survivor.

Henderson² and his collaborators have produced acute effects of oxygen deficiency at sea-level by breathing into an apparatus consisting of a spirometer and a canister containing alkali. The exhaled carbon dioxide is absorbed by the alkali, while the oxygen is gradually diminished by the continual rebreathing. The increase in the frequency of the heart is slight at first, only about one to three beats, but a marked acceleration sets in when the oxygen has fallen to between 13 and 9 per cent. (14,500 to 22,000 feet of altitude). In men who do not tolerate low percentages of oxygen an increase of from 40 to 70 beats was not uncommon. The systolic blood pressure remains about the same until the oxygen has been lowered to between 14 and 9 per cent., when it may rise 15 to 20 mm. Hg above normal. The diastolic pressure remains fairly normal, but falls somewhat after the oxygen has been reduced to 9.5 per cent. or less. The best type of men may tolerate as low an oxygen content as 6 per cent., which corresponds to an altitude of close to 30,000 feet. The hemoglobin showed a well defined increase in at least 25 per cent. of all the men. No cardio-vascular lesions could be noted in men in "optimum" condition; others, on the other hand, developed murmurs and hypertrophic conditions.

In accordance with Bert, it is generally held that the disturbances just described, are due to a failure of the diffusion pressure which

¹ *La nature*, 1875, 337.

² *Medical Studies in Aviation*, Jour. Am. Med. Assoc., lxxi, 1918.

quickly induces a lack of oxygen in the system, commonly called *anoxemia*. This view has found experimental proof in the work of Zuntz and others, who have shown that the oxygen tension in the alveoli is diminished at high altitudes. Upon Monte Rosa, for example, the different members of his party showed tensions of only 37–57 mm. Hg and all suffered from mountain sickness. In this connection attention should briefly be called to the fact that the number of the erythrocytes increases at high altitudes, but clearly, even this change must eventually fail in its purpose for the reason that the tension of this gas finally reaches so low a level that it cannot enter in sufficiently large quantities. The hemoglobin remains below its point of saturation. As a result of this scarcity of oxygen, the heart muscle weakens and eventually fails to sustain the circulation. The nervous tissue is then unable to effect a proper coördination of the muscular movements. Provided, however, that a certain limit has not been exceeded, these symptoms disappear in the course of time and the individual finally acquires a muscular force as great as that previously shown by him upon the plains. This adaptation is dependent upon the production of acid substances, especially lactic acid and carbon dioxide, which exert a stimulating action upon the respiratory center and augment the ventilation in the lungs.

Mosso¹ has submitted a somewhat different explanation which is based upon a diminution in the carbon dioxide tension of the blood, constituting the condition of *acapnia*. The claim is made that mountain sickness is associated with an excessive loss of carbon dioxide in consequence of which the tissues themselves are impoverished. We know, however, that *acapnia* may be present in individuals without that the disorders just mentioned develop, and besides, this condition may be absent during the most acute stage of mountain sickness. It also happens at times that these symptoms appear sometime after the individual has again reached the plains. These facts tend to show that the real difficulty is more deeply seated and must be sought for in a disorder of the tissue oxidations.

Higher barometric pressures are encountered in submarine work, such as is required during the building of tunnels and caissons. It has previously been mentioned that pressures of 5 to 6 atmospheres cannot be endured for any length of time without serious consequences and that a pressure of 15 atmospheres brings on convulsions and death. But, since a depth of 10 m. corresponds to an increase in pressure of only 1 atmosphere, the human body will rarely be called upon to endure a pressure of more than 2 or 3 atmospheres. In descending to this depth it is imperative to proceed slowly, and to permit the system to become adapted first to intermediate degrees of pressure before the chamber of greatest pressure is entered. Quite similarly, it is absolutely necessary to proceed slowly with the decompression, because any abrupt cessation of the pressure is prone to produce a complex of

¹ Der Mensch auf den Hochalpen, Leipzig, 1899.

symptoms which constitute the so-called *caisson disease*,¹ or, as the workmen call it, the "bends." The muscles and joints become painful and a degree of dyspnea develops which leads to cyanosis, congestion, vertigo and unconsciousness. In many cases certain groups of muscles become paralyzed, giving rise to the condition commonly described as "diver's palsy." These symptoms are attributed as a rule to an evolution of nitrogen. Obviously, the absorption of this gas by the tissues increases with the pressure, but if the pressure is then suddenly released, the rapidly escaping bubbles of this inert gas collect in large numbers in the capillaries and cause a blocking of the blood-flow and a loss of function of the parts situated distally to the obstruction. In fact, it is conceivable that the rapid evolution of this gas may lead to an actual destruction of the soft nervous structures and a loss of function of the structures innervated by them.

The Gaseous Composition of the Blood under Different Conditions.

Eupnea.—If the quantities of O and CO₂ in the blood vary within

FIG. 260.—STETHOGRAPHIC RECORD OF THE RESPIRATORY MOVEMENTS.
E, eupnea; A, apnea produced by taking three or four deep breaths.

normal limits, the animal is said to be in the state of eupnea. The respiratory movements exhibit during this period a normal amplitude and frequency.

Apnea.—An animal may be placed in the condition of apnea in two ways, namely, by increasing the frequency of its respiratory movements or by permitting it to breathe pure oxygen. It is a matter of common experience that the taking of two or three deep breaths in rapid succession forces us to suspend our respiratory activity for a short period of time (Fig. 260). Quite similarly, the quickly repeated inflation of the lungs of a tracheotomized animal causes it to cease its respiratory movements temporarily. The inhalation of pure oxygen gives rise to the same effect. As far as the character of the respiratory motions is concerned, apnea signifies a temporary cessation of these movements. With reference to the condition of the blood, several views have been advanced. Thus, it has been thought that this respiratory inhibition is dependent upon an overoxygenation of the blood,

¹ Hill, Caisson Sickness, London, 1912.

this inhibition lasting until the extra amount of oxygen has again been used up. Head,¹ however, has shown that this effect may also be obtained by inflating the lungs with pure hydrogen, although it is true that the apneic cessation of respiration is then briefer in its duration and may, in fact, be abolished altogether. Besides, it should be mentioned that the contention of Ewald, that in apnea the blood is actually oversaturated with oxygen, has been disproved by Hoppe-Seyler.² It seems, therefore, that some other factor, besides the oxygen, must be responsible for this phenomenon. It has been suggested that the repeated distention of the lungs acts as an excitant to the receptors of the vagi nerves, in consequence of which impulses are generated which reflexly inhibit the inspiratory discharges from the respiratory center.³ A more plausible explanation, however, is the one offered by Mosso,⁴ which states that any excessive ventilation of the lungs induces a scarcity of carbon dioxid (acapnia) which eventually leads to a condition of subnormal stimulation of the respiratory center. The respiratory actions then cease until the accumulation of carbon dioxid in the blood has again been raised to normal. That this is so may be gathered from the fact that augmentations of the respiratory movements fail absolutely to produce the apneic standstill if the carbon dioxid content of the inspired air is retained at 4.5 per cent. In order to account for the different discrepancies just enumerated, it has been suggested to recognize three types of apneas, namely:

Apnea vera, which is due to the lowering of the CO₂ content,

Apnea vagi, which is caused by the stimulation of the inhibitor fibers of the vagi nerves, and

Apnea spuria, which is dependent upon stimulations from other parts of the body.

As an example of the first type might be mentioned the apnea fetalis, *i.e.*, the permanent inhibition of the respiratory activity of the young while in the uterus. As an example of the second type may serve the rather temporary inhibition following the distention of the lungs by air or inert gases, and as an example of the third type, the cessation of respiration exhibited by diving animals as soon as their nares or beaks are brought in contact with water.

A very peculiar type of respiration is frequently observed during such pathological states as arteriosclerosis, uremic coma, anemia, increased intracranial pressure and lesions of the central nervous system. The respiratory movements then occur in groups which are separated from one another by apneic pauses. This condition of periodic breathing is commonly designated as *Cheyne-Stokes respiration* (Fig. 261). The periodicity of these movements, however, is not the same in all cases; but whether only ten or forty of them appear

¹ Jour. of Physiol., x, 1889, 1.

² Zeitschrift für physiol. Chemie, iii, 1879, 105.

³ Miescher-Rüsch, Wiener Akad., lxxxv, 1882, 101.

⁴ Arch. ital. de biol., xl, 1903.

together, the first respirations of each group always begin small and gradually increase in amplitude until their maximum has been reached. Subsequent to this point they again decrease slowly to complete stoppage. The intervening respiratory standstills may last only a few seconds or a longer time, say, 30–40 seconds. As Eyster¹ has shown, these variations in the respirations are accompanied by rhythmic changes in the blood pressure, a rise occurring most generally toward the end of the apneic phase, at which time the oxygen tension of the alveolar air is greatly diminished. The succeeding respirations, therefore, would be incited by a lack in oxygen. Pembrey,² on the other hand, advocates the view that the apneic phase is caused by a diminution in the carbon dioxide tension which leaves the respiratory center temporarily without its normal stimulus. At all events, it is possible to remove this condition for a time by the administration of either oxygen or carbon dioxide. The former tends to heighten the

FIG. 261.—TRACING SHOWING THE CHEYNE-STOKES FORM OF RESPIRATION. (Hill.)

irritability of the respiratory center, whereas the latter stimulates it until it again discharges its impulses.

A similar type of respiration is frequently observed during sleep and in meningitis, in which disease it constitutes an unfavorable prognostic sign. It is known as *Biot's respiration* and consists of rapid short breathing which is interrupted by pauses lasting from several seconds to half a minute.

Hyperpnea.—This condition is characterized by a moderate increase in the respiratory rate and amplitude. It is attributed as a rule to a diminution of the oxygen and an increase of the carbon dioxide occurring in the course of heightened muscular activity. Besides the carbon dioxide, it is entirely probable that other fatigue substances are present which act as powerful exciting agents of the respiratory center. It is also possible to augment the respiratory activity in an indirect manner by stimulating the receptors for touch, pain and temperature. A reaction of this kind is usually experienced upon tactile impressions, as well as upon the immersion of the body in water of 32° C. or in water charged with carbonic acid gas. It can also be produced by

¹ Jour. of Exp. Med., viii, 1906, 565.

² Jour. of Path. and Bact., xii, 1908, 258.

exposing an animal to a high temperature or by heating its blood directly as it traverses the carotid artery.¹ These types of hyperpnea, however, are not dependent upon the gaseous composition of the blood and should, therefore, be classified as ordinary reflex reactions.

Dyspnea.—If prolonged, the condition of hyperpnea gradually passes over into the condition of dyspnea, the essential characteristic of which is labored breathing. Its cause lies either in a deficiency of oxygen or in an excess of carbon dioxid; most generally, however, these two factors act in unison. In accordance with this statement, it must be evident that an animal may be rendered dyspneic in two ways, viz., by interfering with its respiratory activity in a mechanical way or by altering the composition of the inspired air. Among the former occurrences might be mentioned the partial occlusion of the respiratory passage by foreign bodies or by pressure from without. In a chemical way, dyspnea may be produced either by lessening the tension of the oxygen or by increasing the tension of the carbon dioxid. The former is designated as $O =$ dyspnea, and the latter as $CO_2 =$ dyspnea. An animal may also be rendered dyspneic by permitting it to breathe an indifferent gas, such as pure nitrogen or hydrogen. Curiously enough, the dyspnea then ensuing cannot be prevented by lessening the carbon dioxid tension of the blood, which would naturally diminish the excitation of the respiratory center. It is also possible to render an animal dyspneic by permitting it to inhale an increased amount of carbon dioxid. In this case, the oxygen cannot be the deciding factor, because the occurrence of this dyspnea cannot be prevented by simultaneously raising the tension of this gas. Deficiencies in oxygen, which finally give rise to dyspnea, may be produced by bleeding, by the fixation of the hemoglobin by carbon monoxid, by hemolysis of the red corpuscles, and by any impairment of the cardiovascular system tending to lessen the vascularity of the tissues.

While the general picture of dyspnea always remains the same, certain differences may nevertheless be noted which allow us to differentiate the $O =$ dyspnea from the $CO_2 =$ dyspnea. The former usually runs a longer course and finally leads to marked motor disturbances. The latter, on the other hand, immediately assumes a more depressive and more narcotizing character. Moreover, during the former the respirations are prone to be rather frequent and display a forced inspiratory character, whereas during the latter they are slow and of a pronounced expiratory type.

Asphyxia.—This condition represents the final state of dyspnea, a state of functional exhaustion and collapse. It signifies that the deprivation of oxygen has been completed. The powerful respiratory movements ordinarily observed during the later stages of dyspnea,

¹ Fick and Goldstein, *Verhandl. math.-naturw. Ges., Würzburg*, ii, 156. The term polypnea has been applied to this form of hyperpnea by Richet, *Compt. rend.*, xcix, 1884, 279.

presently give way to infrequent convulsive efforts and these in turn to slow and shallow respirations and finally to mere spasmodic twitches. At this time, the pupils are markedly dilated, the reflexes are extinct, the integument is cyanosed, and the extremities stiffened. The urine and feces are voided generally before the heart has ceased to beat. The blood pressure rises during the early stage of dyspnea, but falls gradually as soon as the respiratory and cardiac depression has set in. Inasmuch as the heart usually continues to beat for several minutes after the cessation of respiration, it is still possible at this time to resuscitate the animal.

Ventilation.—The problem of ventilation is essentially a physiological one and has to do primarily with the chemical properties of the respiratory air, and secondarily with its temperature and its content in water vapor. Consequently, ventilation provides not only for a continuous supply of pure air in place of that vitiated with the products of metabolism, but also of air possessing a stimulating temperature and a content in aqueous vapor in keeping with the physiological requirements of the body. An undue emphasis, however, should not be placed upon any one of these factors at the expense of the others.

Ventilation does not purpose to bring outdoor conditions indoors, but simply to make indoor conditions fit for indoor life. As far as the composition of the air is concerned, we know that an adult person inspires about 500 c.c. of air seventeen times in a minute and that his output of CO_2 at rest amounts to 17 liters, or to 0.68 cubic feet in an hour. During gentle exertion this value rises to 0.9 and during actual work to 1.8 cubic feet per hour. Assuming then that the normal amount of CO_2 is 0.03 per cent., the percentage of this gas in 1000 cubic feet (28,000 liters) of air will be increased to about 0.1 per cent. in the course of an hour. Obviously, therefore, the amount of fresh air required per hour to keep the CO_2 at 0.06 per cent., is $0.03 : 0.6 :: 100 : x$ or $x = 2000$ cubic feet. If the normal amount of CO_2 is reckoned at 0.04 per cent., 3000 cubic feet must actually be provided for, but naturally, this amount may be supplied in three lots of 1000 cubic feet each. Furthermore, an allowance must be made for the weight of the person, because a woman of 120 pounds exhales only 0.6 cubic feet of CO_2 in an hour and a child of 80 pounds only 0.4 cubic feet. It is also essential to take account of the type of work to be performed by these individuals.

In regard to O_2 , little need be said, because even in the worst ventilated spaces the air seldom approaches a basis of 15 volumes per cent., at which respiration can still go on undisturbedly. Hence, we are chiefly concerned at this time with the CO_2 content of the respired air, but its value should serve merely as a working unit to indicate the degree of vitiation of the air, because even in the worst ventilated rooms it is rarely present in amounts sufficient to exert a pernicious influence. Ordinary increases are endured for some time without discomfort, provided that the temperature and the humidity of the air remain

low. Toward larger amounts of CO_2 , the system very readily reacts by a greater respiratory rate and amplitude and other changes. Thus, if it is said that the air of a room, in which more than 0.07 volume per cent. of CO_2 is present, feels distinctly close and uncomfortable. This sensation should not be referred to a deficiency of O nor to a superfluity of CO_2 , but rather to its temperature, its humidity, and its content in volatile odorous substances and dust.

In poorly ventilated rooms the CO_2 may reach 0.30 volume per cent., and in crowded lecture halls 0.80 volume per cent., but the discomfort experienced in places of this kind may be lessened considerably either by lowering the temperature and the humidity of the air or by fanning it. Even in rooms in which the CO_2 content is 1.0 or 2.0 per cent., no discomforts are experienced so long as the aqueous vapor and the temperature are kept low, but these facts are not cited to minimize the importance of the composition of the air, but solely to show that the other two factors play an important part. In a general way, it may be stated that optimum conditions prevail when the temperature of the room is between 65° and 68°F. , and when the moisture equals 50 to 75 per cent. relative humidity. The air itself should not contain more than 0.06 per cent. of CO_2 and should be as free as possible from bacteria, gaseous admixtures and dust. If it contains more than this amount, artificial means should be resorted to to renew it with a frequency which is to be determined by calculation from the proportion of CO_2 per volume of air.

It seems, therefore, that the injurious consequences of living in poorly ventilated quarters are caused, at least to some extent, by the physical qualities of the respired air, but precisely in what respect a hot and humid atmosphere proves harmful, has not been fully determined. Hermanns¹ has found that the temperature of persons living in very restricted quarters, rises considerably, and furthermore, the results of the New York State Commission on Ventilation² indicate that a high temperature and high humidity give rise to an elevation of the systolic and diastolic pressures, as well as to a diminution of the vascular tonus and a lowering of the resistance of the body against bacterial infections. The general disinclination to exercise experienced at this time, seems to have a deeply seated cause, because the muscles themselves are incapable of performing a normal amount of work. Lee and Scott³ have shown, that a loss of blood sugar results at this time which under extreme conditions may equal 5 per cent. of normal.

¹ Archiv für Hygiene, i, 1883, 1.

² Lee, Science, N. S., xlv, 1916, 183.

³ Am. Jour. of Physiol., xl, 1916, 486.

CHAPTER XLII

THE NERVOUS REGULATION OF RESPIRATION

The Respiratory Center and Its Nervous Connections.—The nervous mechanism concerned in respiration, consists of a center and different efferent and afferent conducting paths. On the efferent side the nerve paths always remain the same, because the same muscles are constantly at work expanding the lung and producing related motor effects. The impulses generated in the respiratory center, reach these different effectors by way of their respective nerves, and hence, the efferent half of the respiratory arc is formed by the different nerves

FIG. 262.—THE NERVOUS REGULATION OF RESPIRATION.

C, respiratory center is under the control of afferent impulses (*A*) from different receptors (*R*). On the efferent side (*E*) it is in connection with the different muscles of respiration (*M*).

innervating the muscles ordinarily concerned in respiration. On the afferent side, on the other hand, conditions are not so simple, because the character of the respiratory movements is subject to variations in consequence of a very large number of sensory impressions. Practically any one of the receptors, internal as well as external, may be the recipient of impressions which are eventually relayed to the respiratory center, where they incite an alteration in the rate and depth of the respirations. In accordance with this brief preliminary statement, it should be evident that the destruction of the efferent paths must entail an immediate arrest of the respiratory movements, because the impulses generated by the respiratory center, are then no longer able to reach the respiratory muscles. An arrest of respiration must also follow the destruction of the center itself, for the reason that the stimuli upon which the contraction of these muscles depends, then fail to materialize. Contrary to these results, the division of the afferent path does not stop the respiratory movements,

because it does not destroy the rhythmic discharges from the center. It is to be noted, however, that the movements are then wholly dependent upon the automatic activity of the center and can no longer be varied by afferent impulses arising in other parts of the body.

The Location of the Respiratory Center.—In accordance with the experiments of Lorry,¹ Le Gallois² and Flourens,³ the respiratory center is situated in the medulla oblongata at the level of the apex of the calamus scriptorius. More recent experiments by Volkmann and

¹ Mémoires prés. a l'acad. des Sciences, i, iii, 366.

² Exper. sur la principe de la vie, Paris, 1812.

³ Rech. exp. sur la systeme nerveaux, Paris, 1824.

others have shown that it is possible to make a median incision through this structure without destroying the respiratory movements. For this reason, the center is said to be bilateral, each half being especially concerned with the muscles situated on the corresponding side of the thorax. In this connection brief reference should also be made to the fact that injuries to the cerebral cortex (hemiplegia) most generally leave the respiratory musculature unaffected. This is especially true of the diaphragm and the intercostals. It seems, therefore, that these muscles, besides being governed by lower centers, possess a bilateral representation in the motor cortex of the cerebrum. Consequently, the destruction of one motor area cannot possibly produce a paralysis of the respiratory muscles, although it gives rise to a unilateral paralysis of the other skeletal muscles.

It might also be stated that several authors have not felt inclined to accept this rather sharp localization of Flourens. Gierke,¹ for example, regards the tractus solitarius as an important part of this center, while Mislowsky² holds a similar view regarding a stretch of gray matter in the vicinity of the hypoglossal nucleus. To be brief, it seems that the respiratory center is not confined to a point-like zone of bulbar gray matter, but occupies a more extensive area, inclusive of its connections with other bulbar centers and the nuclei of important cranial nerves. With Gad,³ it may be assumed that really the entire formatio reticularis enters into the formation of the bilaterally coördinated center of respiration.

A very general localization of this center may be effected in the following way: A deeply anesthetized animal is connected with a stethographic arrangement for recording the respiratory movements. A section is then made transversely through the region of the pons. Inasmuch as the respiratory motions continue after this cut has been made, it is evident that the center is situated in the bulb or spinal cord. A second cross-section is then made below the lower root of the phrenic nerve, at about the level of the sixth cervical vertebra. Since the respiratory movements do not cease even now, it is obvious that the main center is situated above the level of the second cut, *i.e.*, either in the medulla or upper cervical cord. The latter point may now be decided by piercing the lower region of the bulb, when the respiratory motions will cease immediately.

This result may also be obtained by dividing the spinal cord between the main center and the nuclei of the phrenic nerves situated opposite the fourth and fifth cervical vertebrae. In this case, however, the respiratory standstill is not caused by the destruction of the center, but solely on account of its separation from its principal motor apparatus, consisting of the phrenic nuclei and phrenic nerves innervating the diaphragm. Inasmuch as this muscle is absolutely essential

¹ Archiv für Anat. und Physiol., 1893, 583.

² Zentralbl. für die med. Wissensch., 1885, 465.

³ Archiv für Anat. und Physiol., 1893, 75.

to respiration, its isolation and subsequent paralysis would make life practically impossible. This is especially true of young animals. For this reason, it has been advocated to regard the various nuclei of the nerves innervating the different muscles of respiration, as secondary or tributary centers to the main or medullary center of respiration. It does, however, seem scarcely necessary or helpful to look at the respiratory mechanism in this way, because in reality these different nuclei form nothing more than mere stations upon the efferent path and do not possess automatic power. The fact that the respiratory center is situated in the medulla, may also be proved by injuring this structure directly, as may be done by introducing a pointed instrument between the adjoining dorsal borders of the atlas and axis. This constitutes the act of pithing, a procedure which leads to an almost instantaneous stoppage of respiration and a loss of the vascular tonus on account of the destruction of the vasomotor center. The cardiac center is also involved, although the heart itself continues to beat for a brief period of time. Very similar conditions may be produced by sharply bending the head upon the trunk, in which case the odontoid process of the axis may lacerate the bulbar tissue.

The Cause of the Activity of the Respiratory Center.—The foregoing discussion has shown that the respiratory motions are incited at regular intervals by impulses sent out by the center. The question which now presents itself is this: Does this center possess the power of discharging these rhythmic impulses in consequence of an inherent property of its constituents, or does its activity depend upon afferent impulses conveyed to it from other parts of the body? In brief, therefore, it would be necessary to ascertain whether the cells of the respiratory center possess an automatic power, such as is exhibited by the components of the cardiac center, or whether they are activated solely in a reflex way.

It must be conceded that the former view is the correct one, *i.e.*, the rhythm is inherent in these nerve cells and is not generated in a reflex manner. This conclusion is based upon the fact that the center may be completely isolated from the rest of the body by the division of its afferent connections without producing an absolute cessation of the respiratory movements. An experiment of this kind necessitates the division of the brain stem above the medulla and the severance of the vagi and glossopharyngeal nerves. In addition, the spinal cord must be cut across below the nuclei of the phrenic nerves,¹ and must also be rendered impermeable to sensory impulses by dividing the posterior roots in its cervical portion. But even now the objection might be raised that the center cannot be considered as being completely isolated as long as it remains in connection with such efferent nerves as the phrenics, the probability being that these nerves also conduct in a centripetal direction. This contention has been disproved in the following way. Having thoroughly curarized an animal in order

¹ Loewy, Pfüger's Archiv, xlii, 1889, 245.

to paralyze its skeletal musculature,¹ the phrenic nerves were cut and their central ends connected with a galvanometer. It was found that these nerves continued to conduct action currents in a centrifugal direction, clearly indicating thereby a rhythmic activity on the part of the respiratory center. The chemicophysical causes underlying this automatism are wholly unknown; *i.e.*, we have almost no conception regarding the manner in which the metabolic activity of neuroplasm can give rise to a nervous action of this kind.

When speaking of the respiratory center, we frequently lose sight of the fact that this structure has to fulfill a double function, because it activates not only the muscles of inspiration but also those of expiration. To be sure, under normal conditions only the former are brought into play, while the latter remain passive, but conditions may arise at any time which make it imperative to increase the pulmonary ventilation by an active participation of the expiratory muscles. It may be assumed, therefore, that the respiratory center consists in reality of two parts, namely, of an inspiratory and an expiratory. It is conceivable that the function of this entire aggregation of nerve cells is distributed in such a way that the control of the inspiratory muscles is apportioned to some of them, while others are concerned exclusively with the expiratory process. This view may be justified by certain experimental evidence, in spite of the fact that the separate existence of an expiratory center has not been proven. At all events, it is evident that the activity of these cells does not conflict with the function of those controlling the inspiratory mechanism; in fact, it is really subordinated to that of the latter. Thus, active expiratory efforts are invariably made when the venosity of the blood is increased, the purpose of these being to aid the inspiratory mechanism in remedying this condition. In a volitional way, the expiratory mechanism is brought into play during the acts of micturition, defecation, parturition, coughing and sneezing, and in all these instances the inspiratory mechanism is made to conform absolutely to the expiratory. Such an interaction gives rise to the so-called "abdominal press," which plays an important part in the expulsion of the feces and urine.

The Regulation of the Activity of the Respiratory Center.—Since it has been shown that the power of automaticity is restricted to the respiratory center, it should now be evident that the inspiratory movements must cease whenever the muscles expanding the thorax are separated from it. It will be seen, therefore, that the respiratory mechanism differs somewhat from that controlling the activity of the heart, because while the latter organ is also regulated by an automatic center, it possesses the power of continuing its contractions even after it has been separated from the central nervous system. Thus, unlike the respiratory muscles, the heart is capable of developing an automaticity of its own. Keeping these facts clearly in mind, the further statement may now be made that the automaticity of the respiratory center may

¹ Winterstein, Pflüger's Archiv, cxxxviii, 1911, 159.

be varied at any time by conditions arising elsewhere in the body. Moreover, these conditions may affect its activity in two ways, namely, by means of the gaseous constituents of the blood as it passes by its cellular components and secondly, by impulses conducted to it from other parts of the body.

The *chemical regulation of respiration* has a nutritive basis, because it is a well-known fact that an increased venosity of the blood supplying the center immediately leads to an augmentation of the respiratory movements. Conversely, a greater aeration of the blood gives rise to a lessened respiratory frequency and amplitude. It is readily possible to change a dyspneic type of breathing into an apneic type, and *vice versa*. In either case, the question immediately arises, whether the oxygen or the carbon dioxid is the stimulating agent. Thus, it may readily be surmised that the respiratory movements may be rendered dyspneic either by decreasing the amount of the oxygen (Rosenthal), or by increasing the quantity of the carbon dioxid (Traube). The evidence, recently collected by Haldane and his pupils,¹ seems to show that neither one of these factors can be ruled out absolutely. It is very obvious, however, that the center is especially sensitive to changes in the carbon dioxid content of the blood;² in fact, the stimulating potency of this gas is so great that, under normal conditions, the oxygen cannot play an important part in the regulation of respiration. It is true, however, that these two conditions generally go hand in hand, because an increased production of carbon dioxid necessitates a greater intake of oxygen.

In illustration of this statement, it might be mentioned that a decided augmentation of the respiratory movements can only be attained if the oxygen pressure of the alveolar air is reduced from its normal value of 20 per cent. to about 13 per cent. of an atmosphere. In fact, in many instances the subject of the experiment is absolutely unaware of any scarcity of oxygen, although the color of his skin and mucous surfaces clearly betrays a marked deficiency in oxyhemoglobin. Unconsciousness frequently sets in before an augmentation in the respiratory rate has been noticed. Consequently, the action of the oxygen upon the center seems to consist merely in its preventing the accumulation of the products of metabolism by quickly oxidizing them. Whenever this gas is present in insufficient amounts, the cells soon become overloaded with these waste products. This condition increases their irritability so that the carbon dioxid finally acquires a greater potency as a respiratory stimulant.³

Much more decisive results are obtained with carbon dioxid, because an increase in the tension of this gas in the alveolar air of only 2 per cent. suffices to increase the pulmonary ventilation 50 per cent. A rise of 3 per cent. increases it 126 per cent. and a rise of 6 per cent.

¹ Jour. of Physiol., xviii, 1895, 442, and xxxii, 1905, 225.

² Zuntz, Pflüger's Archiv, xcv, 1903, 192.

³ Haldane and Poulton, Jour. of Physiol., xxxvii, 1908, 390.

757 per cent. Furthermore, it is a matter of common experience that the breath can be held for only a brief period of time, obviously because the tension of the carbon dioxid in the blood gradually attains so great a stimulating power upon the respiratory center that it can no longer be subdued by volitional efforts. A longer respiratory standstill may be effected either by taking several deep breaths beforehand or by inhaling pure oxygen. These procedures are intended to remove much of the superfluous carbon dioxid from the lungs and to supply them with enough oxygen to postpone the excitatory influence of the waste products. It is evident, therefore, that the respiratory center is under the direct influence of the blood traversing it. As long as the carbon dioxid tension of the latter remains normal, the respiratory movements retain their eupneic character, while any increase in the tension of this gas is immediately followed by hyperpneic and dyspneic breathing. The tendency is to adjust the depth and frequency of the respiratory movements in such a way that the pulmonary ventilation is always kept the same. Any changes in the gas content of the blood, whether brought about by internal or external causes, affect the center directly and are immediately compensated for by increasing or decreasing its automatic activity.

The *reflex regulation of respiration* is made possible by a multitude of afferent impulses, which take their origin in different receptors. Thus, it is a matter of common experience that the amplitude and frequency of the respiratory motions may be varied not only by sudden changes in the intensity of the light and unusual auditory impacts, but also by sensations of smell, taste, touch, pain and temperature. In addition, the automaticity of the respiratory center may be altered by impulses conveyed to it from the psychic centers of the cerebrum. The latter, therefore, must be classified in large part as volitional discharges which reach this center by way of diverse transcortical paths. To this class also belong the impulses arising in consequence of emotional conditions.

A cold bath most generally produces a deepening and acceleration of the respiratory movements, while the inhalation of irritating emanations leads to an almost instantaneous respiratory standstill. Very similar modifications follow the excitation of the receptors situated in the realm of the splanchnic and sexual organs, but it would lead us altogether too far to discuss these reactions in detail, and besides, their analysis most generally presents no serious difficulty. A certain number of them, however, merit special consideration, because they originate along the pulmonary passage and influence respiration in a most decisive manner. Reference is now had particularly to the acts of sneezing and coughing, resulting in consequence of the excitation of the lining membrane of the nasal, pharyngeal and laryngeal cavities. In accordance with the innervation of these parts, it may be surmised that these reflexes are effected principally with the help of the vagi nerves, which contain afferent as well as efferent respiratory fibers.

Keeping these facts clearly in mind, it is now possible to assign a definite cause to the taking of the first breath. In utero, the respiratory center of the fetus is not subjected to a stimulation by the carbon dioxid, because its blood and tissues are constantly kept in an apneic condition. Subsequent to the obliteration of the umbilical blood-vessels, however, the carbon dioxid accumulates very rapidly and finally incites the center to send out those impulses which give rise to the first respiratory movement. This process is materially hastened by mechanical and thermal stimuli, because the conditions which the fetus meets with during and directly after the period of labor are very different from those to which it has been subjected in utero. It exchanges a practically indifferent medium heated to the temperature of the body, with one much cooler and teeming with mechanical impacts of all sorts.

The Innervation of the Upper Respiratory Passage.—With the exception of a small patch of modified epithelium forming the so-called olfactory area, all sensory impressions from the mucous membrane of the nose are relegated to the system of the *trigeminal nerve*. In accordance with the character of the stimulus, these afferent impulses give rise either to an acceleration or a retardation of the respiratory movements. In the latter case, respiration may be arrested with the chest in either the inspiratory or expiratory position. It need scarcely be mentioned that the impulses generated in the nasal cavity, are first relayed to the respiratory center by way of the trigeminus and are then conveyed to the different muscles of respiration. These stimuli are usually followed by an active expiration, the blast of air being expelled through the nasal cavity, while the oral cavity is temporarily shut off by the closure of the fauces. This constitutes the act of sneezing, the purpose of which is to dislodge the irritating body from the nose.

A similar reflex mechanism for safeguarding the respiratory passage is situated in the pharynx. The lining of this cavity is innervated in a sensory way by the *glossopharyngeal nerves*. Moderate excitations occurring in the realm of these nerves are immediately followed by an inhibition of respiration and an active expiration, but in this case the posterior nares are closed and the expiratory blast of air is expelled through the oral cavity. This constitutes the act of coughing. These impulses from the terminals of the glossopharyngeus are of special value during the act of swallowing, because they lead to a temporary arrest of the inspiratory movement and a closure of the epiglottis so that the food cannot be aspirated into the laryngeal cavity. The path pursued by these impulses is the same as that outlined previously, *i.e.*, they are first relayed to the nucleus of this nerve and to the respiratory center, whence they are directed to the muscles of respiration.

On passing into the cavity of the larynx another nerve is met with, namely, the *superior laryngeal branch of the vagus* (Fig. 263). It is a

matter of common experience that the entrance of a foreign body into the larynx causes an immediate inhibition of inspiration and a forced expiration, the air being ejected in this case through the mouth. It need scarcely be repeated that the impulses generated in this region of the respiratory passage, are first conducted through the nuclei of the vagi nerves to the respiratory center, whence the efferent discharges are diverted to the different muscles of respiration. Obviously, the division of either the right or left superior laryngeal nerve must render the corresponding side of the larynx insensitive to stimulation. Furthermore, inasmuch as this nerve is the only sensory nerve of this organ, the division of both nerves must lead to a complete paralysis of sensation. An animal cannot long survive this procedure, because the gradual accumulation of foreign substances in the upper respiratory passage finally involves the lung tissue and gives rise to an inflammatory reaction which bears the essential characteristics of pneumonia.

While discussing this subject, it might be well to mention that the superior laryngeal nerves are not entirely sensory in their function, but also embrace a number of efferent fibers which innervate the cricothyroid muscles (Fig. 270). Keeping these facts clearly in mind, it will, therefore, be seen that the stimulation of the intact superior laryngeal nerve must produce impulses which (a) pursue an afferent course and give rise to an inhibition of inspiration and a forced expiration, and (b) pass in an efferent direction to cause a contraction of the corresponding cricothyroid muscle. Accordingly, the division of this nerve must induce a loss of sensation on the side of the injury, as well as a paralysis of the corresponding cricothyroid muscle. The stimulation of the distal end of the divided nerve then gives a contraction of the cricothyroid muscle, while the excitation of its central end elicits those sensations which ordinarily produce an inspiratory standstill and forced expiratory blasts of air.

The larynx also receives a second nerve supply by way of the *inferior laryngeal branches of the vagus* (Fig. 263). Since these nerves

FIG. 263.—THE INNERVATION OF THE LARYNX (POSTERIOR VIEW; ONE SIDE).

B, base of tongue; E, epiglottis; A, arytenoid muscles; CA, crico-arytenoid muscle; T, trachea; V, vagus nerve; SL, superior laryngeal nerve; J and O, its inner and outer branches; JL, inferior laryngeal nerve; Br, vagal fibers innervating bronchial musculature.

are given off in the thorax and then return along the trachea to enter the inferior aspect of this organ, they are generally designated as the "recurrent" nerves. They are wholly motor in their function and innervate all the laryngeal muscles with the exception of the cricothyroids. Obviously, therefore, the excitation of this nerve on either the right or left side, must cause a contraction of the muscles in the corresponding half of the larynx, with the exception of the one just mentioned. Accordingly, the division of one or the other of these nerves must lead to a unilateral motor paralysis of this organ, and the division of both nerves, to a bilateral paralysis. Inasmuch as these nerves conduct only in the direction from the center to the larynx and are, therefore, efferent in their function, the excitation of their distal ends must give rise to a contraction of all the laryngeal muscles, with the exception of the cricothyroids. For the same reason, the stimulation of their central ends cannot influence the respiratory rate or amplitude.

The Function of the Vagus Nerve.—The preceding discussion pertaining to the superior and inferior laryngeal branches of the vagus, must lead us to suspect that the cervical portion of the main trunk of this nerve embraces afferent as well as efferent respiratory fibers.

FIG. 264.—STETHOGRAPHIC RECORD OF THE RESPIRATORY MOVEMENTS (DOG) AFTER DIVISION OF THE LEFT (LV) AND RIGHT (RV) VAGI NERVES.

This assumption may be tested experimentally by simply *dividing one or both nerves* above or below the points of origin of their superior laryngeal branches. In either case, this procedure is followed almost immediately by a reduction in the frequency and an increase in the depth of the respiratory movements. The individual movements become pronouncedly inspiratory in their character, and more so, if both nerves have been divided. This change, however, does not necessarily give rise to a dyspneic condition of the animal, because the amount of air furnished by these slow and deep respirations, is practically the same as that previously supplied by the more frequent and shallow movements. It is true, however, that the division of both vagi nerves renders the animal incapable of adjusting itself to different conditions. Thus, if it is made to inhale air containing a large percentage of carbon dioxide, it fails to compensate, owing to its inability to increase its respiratory frequency. Working, therefore, on so small a margin, its pulmonary ventilation soon becomes inadequate for the relief of the high carbon dioxide tension of the blood.

In addition, the procedure of double vagotomy, as the division of both vagi nerves is called, invariably leads to other conditions which are absolutely incompatible with normal function.

Dogs are somewhat more resistant and frequently survive this operation for many days, and in some instances even for an indefinite period of time, whereas rabbits, sheep and horses succumb to it in the course of a few days. In addition to the effects upon respiration and the action of the heart, these animals also exhibit difficulties in deglutition, digestion and assimilation. They lose weight constantly until their lungs eventually consolidate in consequence of a pneumonic affection. Whether this infiltration of the pulmonary tissue is caused by trophic influences or by the ingress of food and bacteria, owing to the functional uselessness of the epiglottis, has not been definitely ascertained.

The division of these nerves should really be effected by the method of freezing rather than by that of cutting, because by this means their power of conduction may be destroyed without the usual initial period of excitation.¹ This accounts for the fact that the diminution in the respiratory activity is commonly initiated by a hyperpneic type of respiration. Furthermore, it should be remembered that these alterations in the frequency and depth of the respiratory movements manifest themselves only if both nerves are cut and that the division of only one nerve generally produces little or no change. Aside from the motor effects evoked with the aid of the inferior laryngeal nerve, the *stimulation of the distal end* of the divided vagus leaves the general character of the respiratory movements unchanged. It should be noted, however, that this nerve also contains efferent fibers for the musculature of the bronchi (Fig. 263). This has been shown by Roy and Brown,² as well as by Einthoven,³ who have found that the excitation of either vagus produces a constriction of the bronchi of both lungs, while the division of either nerve eventually evokes a dilatation of these tubes on the side of the section: It may readily be surmised that these changes in the size of the bronchial passage must lead to variations in the volume of the air contained therein. In this connection it should also be mentioned that the recurrent attacks of dyspnea, characterizing spasmodic asthma, are believed to be associated with spasms of the bronchial musculature. These are said to find their origin in a neuritic condition of the vagus nerve.

The *excitation of the central end* of the divided vagus nerve with a quickly interrupted current may be followed by either a slowing or a quickening of the respiratory movements. The precise character of the effect produced by this procedure depends upon the strength of the stimulus and the irritability of the respiratory mechanism.⁴ To

¹ Gad, Archiv für Anat. und Physiol., 1880, 9.

² Jour. of Physiol., vi, 1885, 21.

³ Pflüger's Archiv, ci, 1892, 367.

⁴ Rosenthal, Archiv für Anat. und Physiol., 1881, 39.

begin with, however, it may be well to state that currents of moderate strength invariably evoke a respiratory standstill in the inspiratory position. This phenomenon is practically identical with that observed upon stimulation of the intact superior laryngeal nerve, or of its central end. Very weak stimuli are prone to develop expiratory tendencies which are usually accompanied by an inhibition of the inspiratory movements. With strong currents the results are perplexing, although it is quite evident that they consist essentially in a respiratory cessation with the chest either in the inspiratory or expiratory position. It need scarcely be mentioned that these effects may also be evoked by the stimulation of the intact vagus.

The Self-regulation of Respiration.—The foregoing experimental data show very clearly that the division of the vagi nerves prevents certain stimuli from reaching the respiratory center which originate along the pulmonary passage and ordinarily tend to increase the activity of these ganglion cells. When no longer under the influence of these afferent impulses, the center falls back upon its inherent automaticity, which gives rise to regular but relatively infrequent impulses. In the second place, it must be concluded that the vagus nerve embraces two kinds of afferent fibers, or rather, afferent fibers which are capable of conducting two types of impulses. One of these inhibits inspiration and the other expiration. Accordingly, it may be conjectured that the inhibition of the inspiratory muscles allows the development of the expiratory process, while the inhibition of the expiratory muscles favors the occurrence of inspiration.

In accordance with this exposition Hering and Brener¹ have formulated the hypothesis that the respiratory movements regulate themselves; *i.e.*, every expiration incites an inspiration and every inspiration an expiration. The vagi, therefore, are regarded as forming the most important link in a check-system which insures a proper sequence and depth of the successive respiratory movements. This leads to a much greater frequency of the respiratory movements than could be obtained if the center alone were the controlling agent. The latter, as has been shown above, possesses a slow rate of discharge. When the lungs are expanded, a stimulus is set up in these organs which travels over the inspiratory fibers of the vagus and eventually stops this movement, permitting expiration to set in. Quite similarly, the deflation of the lungs reflexly incites the subsequent inspiration. Whether these intrapulmonic stimuli are chemical or mechanical in their nature is a much debated question. It seems, however, that the mechanical ones are the most important. They find their origin in the alternate stretching of the vagal terminals which may be imagined to invest the bronchial tubes in the manner of calipers. It should be remembered, however, that the expiratory process is a passive phenomenon and is not associated under ordinary conditions with a contraction of the respiratory muscles, and hence, the inhibiting

¹ Sitzungsab. der Wiener Akad. der Wissensch., cviii, 1868, 909.

fibers of inspiration would not be brought into play during quiet respiration. An activation of the latter, however, would result whenever forced expirations are required to effect a more thorough alveolar ventilation. This mechanism, therefore, insures the perfect regulation of the central discharges so that they develop at perfectly precise intervals, but naturally, it is not concerned with the production of the automaticity of the center.

This hypothesis may be tested in a simple way by suddenly inflating or deflating the lungs. The first procedure is called positive ventilation and is invariably followed by a relaxation of the diaphragm and a long expiratory pause, whereas the second, or negative ventilation, induces a contraction of this septum. Besides, the existence of inspiratory and expiratory fibers in the vagus is also made probable by the effects obtained on stimulation of the intact vagus or of its central end; in fact, Grützner¹ and Langendorf² have proved that the application of a constant current to the vagus results in an inspiratory arrest when descending, and in an expiratory standstill when ascending. In addition, it might be stated that the collapse of the lungs invariably gives rise to a nerve impulse which ascends the vagus and may be registered by means of the string galvanometer. Head,³ moreover, has ascertained that the collapse of either lung produces much more decided inspiratory efforts than the division of both vagi nerves. This he succeeded in showing in the following way: The left vagus of a rabbit having been cut, the corresponding lung was inflated rhythmically by means of a tube inserted in the left bronchus (Fig. 265). The normal action of the right lung was then suddenly interrupted by opening the right pleura. The resulting collapse of this organ incited an immediate tonic contraction of the diaphragm which generally lasted for some time, although the rhythmic inflation of the left organ prevented the occurrence of dyspnea and asphyxia.

FIG. 265.—DIAGRAM TO ILLUSTRATE HEAD'S EXPERIMENT ON THE EFFECT OF COLLAPSE OF THE LUNG.

R.C., respiratory center; R.V., L.V., right and left vagi. (*Starling.*)

¹ Pfüger's Archiv, cvii, 1894, 98.

² Ibid., cix, 1906, 201.

³ Jour. of Physiol., x, 1889, 1.

SECTION XIII

VOICE AND SPEECH

CHAPTER XLIII

THE GENERAL ARRANGEMENT OF THE PHONATING ORGANS

The Larynx.—The production of noises and sounds by animals may be accidental and intentional. Thus, the wings of an insect beating the air at the rate of about 300 times in a second, produce a noise which is merely a phenomenon accompanying muscular action, but animals of this kind are also in possession of certain mechanisms by means of which a simple communication between them is made possible. The latter end they attain by the rubbing together of their hind-legs or by the approximation of their mandibles. In amphibians, the trachea opens anteriorly into the small *laryngeal chamber* which is connected with the cavity of the mouth by a slit-like opening or *glottis*. At one point, the mucous membrane lining this chamber, is folded into two transverse bands, the *vocal cords*, which are made to vibrate by the expiratory blasts of air. In reptiles, the trachea is more distinctly outlined and is expanded anteriorly to form the larynx with its cartilaginous walls and transverse vibrating cords.

Curiously enough, the phonating mechanism of the higher animals differs only slightly from that found in these forms. Its general structural principle, as well as that of several of its minor parts, remains the same. Contrary to this anatomical uniformity, the sounds of these animals gradually attain a greater complexity until they acquire the character of articulated sounds. Thus, vowels and consonants may be distinguished in the notes of birds, which animals have in general a much more extensive register than the mammals. Eventually, the sounds are joined into words and coördinated to give rise to speech. In this regard, man is sharply differentiated from other forms, because practically no other animal is capable of equaling his register of sounds nor his faculty of sound coördination. This difference, however, is not brought about by a relatively much greater structural perfection of his motor apparatus, but rather by a more exclusive development of the association area governing this faculty. In the lower forms the production of sounds is largely a reflex phenomenon. It becomes a complex coördinated act only in those species which are in possession not only of association centers but also of a particular center, having to do solely with the control of the production of sounds. At the present time, however, we are chiefly concerned

with the motor organ, namely, with the larynx and its adjuncts as well as with the nervous paths which connect this organ with the motor area in the Rolandic area of the cerebral cortex. The function of the psychic center for speech and the manner in which afferent impulses are enabled to influence its action, will be discussed later on in connection with the function of the cerebrum and allied parts.

General Structure of the Larynx.—This organ consists of a framework of cartilages held together by ligaments and acted upon

FIG. 266.

FIG. 266.—LARYNGEAL CARTILAGES AND LIGAMENTS, ANTERIOR SURFACE.

1, hyoid bone; 2, 2, 3, 3, greater and lesser cornua; 4, thyroid cartilage; 5, thyrohyoid membrane; 6, thyrohyoid ligaments; 7, cartilaginous nodule; 8, cricoid cartilage; 9, the cricothyroid membrane; 10, the cricothyroid ligaments. 11, trachea. (*Sappey*.)

FIG. 267.

FIG. 267.—LARYNGEAL CARTILAGES AND LIGAMENTS, POSTERIOR SURFACE.

1, 1, thyroid cartilage; 2, cricoid cartilage; 3, 3, arytenoid cartilages; 3, 4, crico-arytenoid articulations; 5, 5, cricothyroid articulations; 6, union of the cricoid cartilage and of the trachea; 7, epiglottis; 8, ligament uniting it to the reentering angle of the thyroid cartilage. (*Sappey*.)

by a system of extrinsic and intrinsic muscles. The following cartilages enter into its formation:

Single cartilages

Thyroid
Cricoid
Epiglottis

Paired cartilages

Arytenoid
Cornicula laryngis
Cuneiform

But even in the case of the single cartilages, a certain tendency toward bilateralism is unmistakable, because they are thickest and most extensive at the sides of the larynx and are united in front by merely a narrow bridge of connecting tissue. These cartilages are adjusted upon the anterior extremity of the trachea in such a way that a relatively large cavity is formed which is protected against the pharynx by the epiglottis. Its pharyngeal aperture is triangular in shape, its base being directed forward and its apex backward.

The larynx as a whole, as well as the trachea, is movable, because it is suspended from the hyoid bone by the thyrohyoid muscles. This bone in turn is affixed to the base of the skull and the maxilla by a number of muscles, and is therefore also freely movable. The upward movement of the larynx is counteracted by the sternothyrohyoid muscles which unite this organ with the sternum. The

FIG. 268.—VERTICAL TRANSVERSE SECTION OF THE LARYNX. (After Testut.)

1, posterior face of epiglottis, with 1', its cushion; 2, aryteno-epiglottic fold; 3, ventricular band, or false vocal cord; 4, true vocal cord; 5, central fossa of Merkel; 6, ventricle of larynx, with 6', its ascending pouch; 7, anterior portion of cricoid; 8, section of cricoid; 9, thyroid, cut surface; 10, thyrohyoid membrane; 11, thyrohyoid muscle; 12, aryteno-epiglottic muscle; 13, thyroarytenoid muscle, with 13', its inner division, contained in the vocal cord; 14, cricothyroid muscle; 15, subglottic portion of larynx; 16, cavity of the trachea. (American Text-book of Physiology.)

larynx may be displaced for a distance of several centimeters, first in consequence of the muscular activity coincident with the act of swallowing and secondly, in consequence of the adjustment of the laryngeal parts for purposes of phonation. In the former case, the larynx is also tilted forward, insuring a greater prominence of its anterior border.

In longitudinal section the laryngeal cavity exhibits the shape of an hour-glass, the true vocal cords forming the line of demarcation between its upper and lower recesses. Moreover, while the long axis of its upper recess is directed strongly backward, that of the lower conforms more closely to the general course of the trachea. The *thyroid cartilage* forms the front and sides of the upper part of the larynx. It is composed of two nearly square plates which are placed vertically and are united in front by a bridge which gives rise to a prominence, known as the *pomum Adami*. Posteriorly, they are rather widely separated from one another, the intervening space being filled by soft tissues. The *cricoid cartilage* forms a heavy ring which completely surrounds the lower cavity of the larynx. It is narrow in front, but

broadens out posteriorly into a quadrate plate. The latter is narrowed above into a pointed process. The *arytenoid cartilages* are two irregular, triangular plates, the bases of which are placed transversely upon the superior processes of the cricoid. The *corniculæ laryngis* are two small cone-shaped cartilages which are fastened to the upper pro-

jection of the arytenoids. The *cuneiform cartilages* are placed within the aryteno-epiglottidean folds.

The Function of the Epiglottis.—The larynx is protected against the digestive tract by a leaf-like plate of yellow elastic cartilage which is attached below by a stalk to the thyroid cartilage. In the adult it usually assumes a nearly vertical position, while in children it is placed more slantingly. It has a double purpose, namely, to prevent the ingress of food into the respiratory passage and to aid in the modification of the currents of air during respiration and phonation.

The closure of the pharyngolaryngeal opening, however, is not effected solely by the epiglottis, because a rather efficient occlusion of this orifice is also had when this structure is wanting or is imperfectly developed. Neither is it correct to assume that those muscle fibers which arise upon the thyroid and are inserted upon the epiglottis are sufficiently powerful to serve as sphincters.¹ A third factor must be taken into consideration, and that is the elevation and forward inclination of the entire larynx. This movement gives rise to an approximation with the hyoid bone so that the tongue, when drawn back during the act of swallowing, is in the best possible position to press the epiglottis downward until it comes to lie across the laryngeal aperture. At this very moment, the thyro-epiglottidean muscle fibers contract, thereby tending to constrict this orifice. It is also held that the epiglottis serves as a sort of sounding board against which the vibrating particles of air are forced. Thirdly, its partial closure upon the forced expiratory blasts gives rise to the peculiar fragmented character of the current of the air produced during the act of coughing. When acting upon the inspiratory current of air, its partial closure gives rise to such peculiar modifications as are noted during the act of hic-coughing. The fact that the mucous lining of this structure is beset with numerous taste-buds and glands does not possess a special functional significance.

The True and False Vocal Cords.—When looked at from above, the wide expanse of the laryngeal cavity is seen to be limited by two membranous bands, the *vocal cords*, which extend transversely across its lumen in a direction from before backward. The space between these bands is known as the *glottis*. The size and shape of the latter vary with the respiratory movements and phonation. During inspiration it becomes large and during expiration small. When the vocal cords are widely separated, its width measures about 13.5 mm. in men and 11.5 mm. in women. During phonation it usually assumes the shape of a mere slit, designated as the chink of the glottis, or *rima glottidis*.

The true *vocal cords* arise in front from the angle formed by the alæ of the thyroid cartilages, and, passing directly backward, are inserted upon the vocal processes of the arytenoid cartilages. They

¹ Meltzer, The Closure of Glottis During Deglutition, *Zentralbl. für Physiol.*, xxvi, 1912.

vary in length in men from 15–20 mm. (average 18.22 mm.) and in women from 10–15 mm. (average 12.6 mm.). Their free edges are thin and tilted slightly upward, while their outer margins are straight and are everywhere adherent to the wall of the larynx. The yellow elastic fibers composing their substance, are closely interwoven and pursue in general a longitudinal course. Of functional importance is also the fact that these bands are covered with thin, flat, stratified epithelium, while the remaining extent of the larynx is lined with columnar, ciliated epithelium. The effective stroke of these cilia is executed toward the pharynx, *i.e.*, in the same direction as that of the cilia found in the trachea and bronchi.

The space above the vocal cords is known as the *supraglottic cavity*. It is bounded above by the epiglottis. On each side of the

FIG. 269.—THE LARYNGOSCOPIC IMAGE IN EASY BREATHING. (Stoerk.)

1, Base of the tongue; 2, median glosso-epiglottic ligament; 3, vallecule; 4, lateral glosso-epiglottic ligament; 5, epiglottis; 6, cushion of epiglottis; 7, cornu major of hyoid bone; 8, ventricular band, or false vocal cord; 9, true vocal cord; opening of the ventricle of Morgagni seen between 8 and 9; 10, folds of mucous membrane; 11, sinus pyriformis; 12, cartilage of Wrisberg; 13, aryteno-epiglottic fold; 14, rima glottidis; 15, arytenoid cartilage; 16, cartilage of Santorini; 17, posterior wall of pharynx. (*American Text-book of Physiology.*)

latter a fold of mucous membrane extends obliquely downward and backward, forming the lateral boundary of the aperture of the larynx, and covering the arytenoid cartilages. Besides these *aryepiglottic folds*, the mucosa of the larynx also presents two transverse ridges, one on each side, which are known as the false vocal cords. These relatively narrow bands are situated a short distance above the true vocal cords and are placed practically parallel to these, so that a long slit-like space is left between them. The function of these bands is not fully understood, but it has been assumed that they serve to protect the true vocal cords against injury and excessive vibration. In the second place, it is held that they serve as sphincters of the larynx, their approximation tending to render the corresponding movement

of the true vocal cords more effective. Special use is made of this mechanism, in conjunction with the closure of the epiglottis, whenever large amounts of air are to be temporarily retained in the lungs, or when, as in running, the outflow of the expiratory air is to be retarded. Thirdly, inasmuch as their mucous covering contains numerous mucous and serous glands, it is also believed that they furnish the moisture necessary to keep the vocal cords in a proper condition for vibration. This secretion is temporarily retained in the capillary space between the true and false cords and is in this way protected against evaporation. In some of the lower animals, these spaces which are called the *ventricles of Morgagni*, are very commodious and are constructed in such a way that they may serve as resonating chambers. This peculiarity in their general arrangement has led to the belief that they tend to augment the vibration of the true vocal cords.

The Tension of the True Vocal Cords.

—The thyroid and cricoid cartilages articulate by means of a simple bilateral joint, the axis of which is placed transversely. Arising upon the anterolateral aspect of the cricoid, a small conical muscle, known as the cricothyroid, passes upward and backward to be inserted upon the lower edge of the alæ of the thyroid (Fig. 270). Its function is to diminish the height of the space between the inferior border of the thyroid and the upper border of the cricoid cartilages. This end it attains by depressing the former and raising the latter. The result of this movement is made evident immediately if it is noted that these cartilages are hinged posteriorly (*R*) and that the arytenoids (*A*), which are situated transversely upon the tips of the cricoid processes, are thereby moved farther backward. It will be remembered that the vocal cords (*VC*) are attached to the anterior tips of these cartilages and extend from here directly across the cavity to be inserted upon the anterior wall of the larynx. Obviously, therefore, since the approximation of the thyroid and cricoid cartilages increases the distance between the vocal processes of the arytenoids and the anterior wall of the larynx, these bands must be put on the stretch. Thus, it is evident that the aforesaid muscle serves as the tensor of

FIG. 270.—LATERAL VIEW OF LARYNX TO ILLUSTRATE THE ACTION OF THE CRICOTHYROID MUSCLE.

H, hyoid bone; *M*, thyrohyoid membranes; *PA*, pomum Adami; *T*, thyroid cartilage; *C*, cricoid cartilage; *Tr*, trachea; *CT*, cricothyroid muscle; *P*, vertical plate of cricoid with (*A*) arytenoid cartilages placed transversely upon its articulating processes; *VC*, vocal cords; *R*, imaginary center of rotation of cricoid. When cricothyroid muscle contracts, *T* and *C* are brought closer together, while *A* is forced away from *PA*.

the vocal cords, and that the mechanism just described is the one ordinarily made use of in raising the pitch of the sounds. The approximation of these cartilages may be felt by placing the finger in the notch below the pomum Adami while sounds of different pitch are produced. In the human larynx, the vocal cords are penetrated by a few muscle fibers which take their origin upon the arytenoid cartilages and eventually reach the anterior wall of the larynx. Their contraction is said to render the vocal cords more tense and hence, this muscle, which is known as the tensor vocalis, is commonly regarded as an aid to the cricothyroid. Grützner,¹ on the other hand, believes that its contraction renders these bands more flabby and forms, therefore, a typical detentioner. Nagel² adheres to the first view and states that these muscle fibers antagonize the lateral displacement of the edges of the vocal cords, thereby retaining them more fully in the path of the expiratory currents of air.

The Approximation of the Vocal Cords.—As has been stated above, the musculature of the larynx is arranged in a manner to form a sphincter for the upper end of the respiratory passage, the closure of which is really effected at three different levels, namely, at the epiglottis, at the false vocal cords and at the true vocal cords. The first two actions having been discussed, we are now in a position to analyze the third, namely, the adduction and abduction of the vocal cords.

The arytenoid cartilages are two triangular platelets which are placed transversely upon the tips of the cricoid processes. They attain their greatest width posteriorly, while their tapering extremities or vocal processes, are directed forward to serve as points of attachment for the vocal cords. Furthermore, while their anterior processes are freely movable in a transverse direction, their basal portions are relatively fixed, because they form articulations with the vertical plates of the cricoid cartilages. The latter, as has been shown by Stieda and Will,³ are prolonged upward into two small cylindrical projections, the convex surfaces of which are turned upward to fit into corresponding concavities upon the under surfaces of the arytenoid cartilages. These joints are adjusted in such a way that the outward movement or abduction of the vocal processes necessitates a slight elevation of these cartilages, while their inward movement, or adduction, permits them to reassume their former low level. By inference, it may then be concluded that the adduction of the arytenoid processes brings the vocal cords closer together, while their abduction separates them more widely. Consequently, the glottis assumes a mere slit-like outline during the former movement and a typical V-shaped outline during the latter. It should also be observed that the approximation of the vocal cords is greatly facilitated by an inward movement

¹ *Ergebn. der Physiol.*, i, 1902, 466.

² *Handb. der Physiol.*, iv, 1909, 702.

³ *Dissertation*, Königsberg, 1895.

of the arytenoid cartilages as a whole, which brings their posterior extremities closer together.

The muscles involved in this process belong to the intrinsic group of the laryngeal musculature, and present the following individual actions:

(a) *The posterior crico-arytenoid muscle* arises from the posterior surface of the quadrate plate of the cricoid cartilage on either side of the median line and passes obliquely upward and outward to be inserted upon the external angle of the muscular process of the arytenoid cartilage (Fig. 271, 1). Its chief action is to rotate the vocal process of the corresponding arytenoid upward and outward so that the glottis is widened. This muscle, therefore, abducts the vocal cords.

(b) *The lateral crico-arytenoid muscle* takes its origin upon the upper border of the cricoid cartilage and, passing upward and backward, is inserted upon the forepart of the muscular process of the arytenoid (Fig. 271, 2). Its contraction gives rise to an inward and downward movement of the vocal process, insuring thereby an adduction of the vocal cords chiefly at their posterior ends.

FIG. 271.—DIAGRAM ILLUSTRATING THE ABDUCTION AND ADDUCTION OF THE VOCAL CORDS.

A, abduction; 1, point of insertion of the post. crico-arytenoid muscle; G, glottis; B, adduction; 2, points of insertion of the lat. crico-arytenoid and thyro-arytenoid muscles; 3, point of insertion of the arytenoid muscles. The dot indicates the position of the center of rotation of the arytenoid cartilages.

(c) *The thyro-arytenoid muscle* extends between the inner surface of the thyroid cartilage, post-external to the median line, and the anterior margin and external angle of the arytenoid. Its inner fibers lie in close relation to the vocal cords and are frequently designated as the musculus vocalis. When contracting, this muscle rotates the corresponding arytenoid cartilage around its vertical axis, drawing the vocal process forward and inward. It acts, therefore, as an aid to the lateral crico-arytenoid muscle in causing the adduction of the vocal cords.

(d) *The arytenoid muscle* extends from side to side, joining the two arytenoid cartilages. It consists of two groups of fibers, one of which is directed horizontally across the median line and the other obliquely (Fig. 271, 3). The ends of the former are fastened to the outer margins of the arytenoids on each side, while the latter unite the outer angle of one with the apex of the other. Obviously, these fibers have to do with the approximation of the posterior ends of the arytenoid cartilages, lessening the length of the rima glottidis.

The Innervation of the Larynx.—The nerve supply of the larynx is derived from the systems of the right and left vagi nerves. The

particular branches which govern the function of this organ are the superior and inferior laryngeal nerves (Fig. 263). In general it may be said that their innervation is unilateral in character, but a slight median overlapping, especially with regard to the sensory fibers, is not uncommon. It has been shown above that the superior branches are motor as well as sensory in their function, while the inferior or recurrent branches are wholly motor. The motor qualities of the former are restricted to their rami externi which supply the cricothyroid muscles. These muscles, as we have just seen, govern the vertical approximation of the thyroid and cricoid cartilages and determine, therefore, the tension of the vocal cords. Consequently, it may be stated that the inferior branches control all the muscles of the larynx with the exception of the cricothyroids.

Keeping these facts clearly in mind, it must be evident that the stimulation of the intact superior laryngeal nerve, or of the distal end of the divided nerve, leads to an approachment of the thyroid and cricoid cartilages and an increased tension of the vocal cords. The glottis is slightly narrowed by this action, owing to the fact that the arytenoid cartilages are not sufficiently resistant to withstand the pull exerted by the vocal cords. The cricothyroid muscle as such, however, does not serve as an adductor of the vocal cords. As has been stated in one of the preceding paragraphs, the sensory qualities of this nerve may be ascertained by the stimulation of the intact nerve or of its central end. With currents of moderate strength, this procedure evokes a respiratory standstill and forced expiratory blasts.

Certain evidence has been presented to show that the inferior laryngeal nerve of the apes also conducts in an afferent direction. This is also true of the corresponding nerve in the dog and cat, but only under special conditions. In view of this uncertainty, it seems best to regard this nerve essentially as a motor path for those impulses which give rise to the different sphincter actions of the larynx, and especially to that occurring at the level of the vocal cords. Attention should also be called to the fact that the vagus innervates extensive segments of the pharynx and esophagus and is thus placed in a position to correlate the action of the laryngeal musculature with that of the muscles used during the process of deglutition.¹

In accordance with these statements, it may be concluded that the division of either inferior laryngeal nerve must lead to a paralysis of the muscles on the corresponding side of the larynx, excepting, of course, the cricothyroid muscle. Quite similarly, the division of both nerves must result in a bilateral paralysis, the aforesaid muscles being excepted. In young animals, this procedure is usually followed by serious symptoms, death from asphyxia resulting in the course of a few days. But, while it is true that the vocal cords assume an extreme median position in consequence of the paralysis of the arytenoid muscles, this condition cannot be regarded as the sole cause of

¹ Schultz and Dorendorf, *Archiv für Laryngologie*, xv, 1904.

death. Account must also be taken of the fact that the accompanying paralysis of the esophageal musculature leads to an accumulation of food and fluids which eventually find their way into the respiratory channel. Consequently, the division of the inferior laryngeal nerves paralyzes that mechanism by means of which the lungs are ordinarily protected against foreign bodies and injurious emanations. Suffocation or pneumonic conditions are the usual outcome of this defect. Very similar results may be obtained by the division of the superior laryngeal nerves, because this procedure blocks those afferent impulses which normally evoke the act of coughing, thereby dislodging the foreign material from the larynx.

By selecting the highway of the vagus, these sensory impulses eventually reach the nucleus of this nerve in the medulla, whence they are relayed to other centers and finally to the motor area in the cerebral cortex. Those movements of the larynx which are associated with respiration, are automatically controlled by a center situated in the medulla and closely allied to the respiratory center.¹ Motor points for the laryngeal muscles have been isolated by Krause² in the gyrus præfrontalis. It will be pointed out later on during the discussions upon cerebral localization, that these motor points are under the control of a psychic center for phonation and speech, which is situated in part in the left inferior frontal convolution.

CHAPTER XLIV

PHONATION

In order to be able to produce a sound, it is necessary to be in possession of a vibrating body the constituents of which may be set into an alternating motion by some external force. In the higher animals, the chief vibrating bodies are the vocal cords, while the power to make them oscillate is most commonly supplied by an expiratory blast of air which may be softened or intensified by muscular activity. Moreover, since these expiratory blasts are directed not only against the vocal cords but also against other mucous folds and membranous septa, noises and sounds of practically all descriptions may be obtained. It is true, however, that those sounds which are ordinarily coördinated into speech, are chiefly dependent upon the vibration of the vocal cords, while the parts above and below them serve merely to modify the primary sound. In this regard man possesses a decided advantage, because the different parts of the human larynx are more delicately adjusted and are under the direct control of an intricate system of motor

¹ Grossman, *Zentralbl. für Physiol.*, iii, 1889.

² *Archiv für Anat. und Physiol.*, 1884.

and sensory centers. Thus, the production of coördinate vocal sounds is really a distinguishing characteristic of man; no other animal can at all equal his power of phonation.¹ Some seemingly authentic cases, however, are on record which show that speech of a very crude and limited type may also be acquired by other mammals, and quite aside from the "talking horse" and "talking dog," it seems that the monkeys and apes have a limited register of words, conveying different meanings.

The Examination of the Larynx in Reflected Light.²—In animals the play of the laryngeal parts may be studied without much difficulty by direct inspection. A transverse incision having been made between the hyoid bone and the upper edge of the thyroid cartilage, the larynx is raised upward and tilted sufficiently to allow an unobstructed view

FIG. 272.—DIAGRAM OF LARYNGOSCOPE. (From Stewart's "A Manual of Physiology," William Wood and Co., Publishers.)

of the supraglottic cavity and especially of its floor formed by the vocal cords. Killian³ has devised a method of transillumination by means of which the larynx may be projected in magnified form upon a screen. The human larynx may be inspected with the help of a small plane mirror which is mounted upon a handle and is placed obliquely against the uvula. A beam of light is then reflected upon it from a head mirror (Fig. 272). The observer looking through a small central opening in the latter, obtains an image of the parts below, but those normally situated in front, appear in the picture to be located behind, and *vice versa*.

The white glistening vocal cords are sharply outlined against the red mucous lining of the rest of the laryngeal wall (Fig. 268). During

¹ Mott: The brain and the voice in speech and song, New York, 1910, and Aikin, The voice, an introduction to practical phonology, London, 1910.

² First successfully undertaken in 1854 by M. Garcia, a teacher of singing. In 1857 Türk employed this method upon his patients in Vienna.

³ Münchener klin. Wochenschr., No. 6, 1893.

quiet respiration, the glottis is moderately large, becoming smaller on expiration. Moreover, by forced inspiratory efforts, the size of this communication may be increased in such a measure that the upper rings of the trachea, and even the bifurcation of the bronchi, are brought into view. Movements of the vocal cords also result in consequence of various accessory respiratory efforts, such as are made necessary during the acts of coughing, sneezing, and hiccoughing.

The production of sounds requires not only a varying approximation of the vocal cords, but also a very precise adjustment of their tenseness. The former effect which, as has been pointed out above, is based upon the rotation of the arytenoid cartilages around their vertical axes, seems to constitute a more accurate mechanism than the latter which is largely dependent upon the backward movement of these cartilages in consequence of the contraction of the cricothyroid muscles.

The different laryngeal parts having been properly set, the air stored in the lungs is forced outward through the narrow glottis, thereby imparting a vibratory motion to the vocal bands. In order to overcome the resistance interposed at this level, it has been found that the air-pressure in the trachea necessary to cause a sound of ordinary pitch and loudness, must be raised to between 140 and 240 mm. of water. Loud sounds require a pressure of as much as 950 mm. of water. It should also be remembered that the vibrations are not restricted to the vocal cords, but are also transferred to the air contained in the outer respiratory passage as well as to that filling the trachea and bronchi. Thus, we speak of a chest voice and a falsetto voice. Chest sounds always impart a fremitus to the wall of the thorax which may be perceived by placing the hands over the lower air-passage, from which the resonance is obtained. Falsetto sounds derive their resonance principally from the pharyngeal, oral and nasal cavities. In general, therefore, it may be said that the vocal mechanism embraces: (1) the motive expiratory blast of air, (2) the larynx which gives rise to the fundamental sound, (3) the thorax, pharynx, mouth and nose which modify the primary sound and give color to it, and (4) the organs employed in articulating the sounds.

The Characteristics of Sounds.—The action of the vocal cords may be imitated in a crude way by placing a short tube of a diameter of about 2 cm. against the palmar surfaces of two adjoining fingers. By blowing into the free end of this tube a sound will be produced in consequence of the vibrations of the folds of skin along the two fingers. A similar purpose is served by the so-called artificial larynx which consists of a piece of tubing, one end of which is partially closed by,

FIG. 273.—POSITION OF VOCAL CORDS ON UTTERING A HIGH NOTE. (*Landois.*)

two bands of animal membrane. Appliances of this kind, however, do not give a correct picture of the action of the vocal cords, because the vibratory parts of these models consist of closely approximated bilipped membranes which oscillate toward one another. Nevertheless, they serve the useful purpose of demonstrating that the vocal sounds, in agreement with the sounds produced by any musical instrument, differ from one another in loudness, pitch and quality.

The *loudness* or intensity of a sound is determined by two factors, namely, the volume and force of the expiratory blast of air and the amplitude of the vibrations of the vocal bands in either direction from their position of rest or equilibrium. These vibrations, moreover, are greatly reinforced by the sympathetic oscillation of the walls of the chest and head parts.

The *pitch* of a sound depends upon the number of vibrations occurring in a unit of time. Obviously, therefore, it is determined first of all by the character of the vibrating body, *i.e.*, by the length, thickness and general elastic qualities of the vocal cords. Secondly, it is dependent upon the degree of tension to which these bands are subjected, the highest sounds being emitted when they are tightly stretched beside a narrow glottis. As a rule, the outline of the latter remains elliptical as long as the vibrations do not exceed 240 to the second. Between 240 and 512 vibrations, on the other hand, the vocal bands are gradually brought closer together until they eventually envelop merely the narrowest possible slit. In fact, the production of very high notes requires an almost absolute approximation of these bands so that only short segments of them are allowed to vibrate. At this time, the vocal aperture or rima vocalis is restricted to a small oval opening situated directly behind the anterior wall of the thyroid cartilage.

The foregoing very general reference to the structural peculiarities of the vocal cords may serve as an explanation for the differences in the pitch and quality of the voice in men and women. Since the vocal bands of children are relatively short, the pitch of their voice must be high. At puberty, however, the larynx develops very rapidly in both sexes, a fact which readily accounts for the rather sudden drop in the pitch of the voice occurring at this time. Moreover, owing to the fact that the cords attain a greater length in men, this "breaking" of the voice is especially pronounced in them. In most instances, the voice of women acquires at this time merely a fuller and richer character. If the development of distinct sex characteristics is prevented by castration or by disturbances in the function of the internal secretory organs, the larynx fails to undergo these changes and the voice retains its peculiar high pitch and immature quality.

The *quality* of the sounds depends upon the character of the vibrations. Like in any musical instrument, the vibrations of the vocal cords are of the composite type, *i.e.*, they are made up of fundamental

and secondary oscillations. In the first instance, the cords as a whole swing to and fro, while in the second, only short segments of them are made to vibrate. In this way, the fundamental tone is constantly combined with secondary partial tones or overtones. Besides, the laryngeal sounds are qualified by the resonance of the chambers situated above and below, and especially by the oral and nasal cavities.

The Peculiarities of Vocal Sounds.—The musical sounds which we are capable of producing, do not shade evenly into one another from the lowest to the highest, but appear in groups, *i.e.*, a number of them always possess a quality which is often sharply differentiated from that of the neighboring group. We speak, therefore, of vocal registers, but it must be remembered that the “breaks” between these may be rendered less conspicuous by training. It is commonly stated to-day that the range of the voice embraces two registers, namely, the chest voice and the falsetto. Some authors also recognize a third, or middle register, and some even a fourth. As may be surmised, these differences depend upon modifications in the use of the resonating parts. The chest-register is the lowest and is produced by a pronounced vibration or fremitus of the wall of the thorax. It is richer in overtones, and requires somewhat smaller quantities of air, because the vocal bands are more closely approximated than they are during the production of the falsetto or head-notes. Inasmuch as the latter depend principally upon the resonance of the cavities of the head, their production requires a copious supply of air which is made to escape through the anterior part of the rima glottidis, while the posterior portion of the glottic space remains closed.

A fundamental difference between the voice used in *talking* and that employed in *singing*, does not exist. During singing, however, certain qualities of the sounds are intensified chiefly by rendering the path of the sound-waves perfectly free so that they are enabled to attain sonority and a greater penetrating power. This is especially true of the vowels, the fundamental note of which is always protected as much as possible against admixtures or formants. Moreover, in singing, the individual notes are not maintained for so long a time as in talking.

Under ordinary conditions the *range of the singing voice* extends over two octaves, but it can be considerably increased by training so that it finally embraces 3 or $3\frac{1}{2}$ octaves.¹ In *whispering* the vibrations of the vocal cords are displaced by friction sounds produced along the laryngeal and buccal pharyngeal walls. The vocal bands are rather relaxed at this time, while the glottis is made to assume an intermediate size.

Speech is articulated voice. The voice sounds are modified by the resonance of the different chambers and are combined with noises

¹ Gutzmann, *Stimmbildung und Stimmpflege*, Wiesbaden, 1906; also Roudet, *Éléments de phonétique générale*, Paris, 1911.

produced outside the larynx. Thus, we obtain vowels or sonants and consonants. The former are dependent upon the vibrating qualities of the vocal cords and are, therefore, musical sounds, while the latter are noises caused by irregular oscillations of the mouth parts. One of these extralaryngeal constrictions, against which the expiratory current of air is forced, is formed by the lips, another by the teeth and the tongue and still another, by the soft palate and the tongue.

While the fundamental character of the *vowels* is determined by the vibration of the vocal cords, a special quality is imparted to them by the varied resonance of the oral cavity. Such factors as the size and shape of this cavity, the position of the tongue and the shape of the soft palate play a part in their formation. Their influence is chiefly directed toward the reinforcement of certain overtones. This view which is essentially the one advocated by Helmholtz,¹ has been modified somewhat by Hermann,² who claims that the mouth does not act as a mere resonator, but actually gives rise to secondary musical notes which need not be harmonics of the laryngeal sound.

As has just been stated, the *consonants* are produced by the various constrictor adjustments of the mouth-parts, *i.e.*, by "positions of articulation." In accordance with the seat of the obstruction, these sounds are classified as labials, dentals, gutturals and nasals. Every one of them may be characterized as soft and hard, the former designation being applied to them if they are formed during phonation and the latter if the vocal cords do not take part in their production. The sound D, for example, is a soft dental sound, because the simultaneous vibration of the vocal cords gives it quality, while the sound T is hard, because it is a pure dental sound and is not accompanied by phonation. Grützner has divided the consonants into *semivowels*, *explosive and friction sounds*. Among the first may be mentioned the sounds *m*, *n*, *ng*, *l* and *r*. Thus, if sounded in part through the nose, as "resonants," as in *him*, *hen*, or *being*, they assume the character of vowels, because they are produced by the vibration of the vocal cords, while the air is forced out largely through the nasal cavity imparting to them a peculiar nasal resonance. But if employed as real consonants, as in *make* or *no*, they acquire the characteristics of explosive sounds. Typical explosives are the sounds *p* and *v* (labials), *t* and *d* (linguopalatals or dentals) and *k* and *g* (gutturals). They are said to be formed with or without voice, because the production of some of them necessitates a vibration of the cords, for example, the sounds *b*, *d* and *g*. Friction sounds or frictionals, are produced by the passage of the expiratory air across the edges of constricted areas, which are thereby thrown into vibration. In this way, there are produced at the labio-dental communication the sounds of *f*, *v*, and *w*; the first of which does

¹ Lehre von den Tonempfindungen, Braunschweig, 1877.

² Pflüger's Archiv, xlvii, 1890, 44.

not require voice, while the other two do. As lingual frictional may be classified such sounds as *s*, *th*, *sh*, *ch*, *z* and *j*, the production of the last two necessitating phonation. The vibrative *r* is produced entirely with the tongue, while *h* finds its origin at the pharyngeal entrance. In the latter case the mouth-parts assume the position ordinarily required to utter the vowel following the *h*, as in *hear* or *house*.

PART V

THE CENTRAL NERVOUS SYSTEM

SECTION XIV

THE FUNCTIONAL SIGNIFICANCE OF THE NERVOUS SYSTEM

CHAPTER XLV

THE STRUCTURAL ARRANGEMENT OF THE NERVOUS SYSTEM

The Subdivisions of the Nervous System.—Topographically the nervous system presents itself as a *central mass*, consisting of the cerebrum, cerebellum, basal ganglia, medulla and spinal cord, and a *peripheral complex*, formed by the cranial, spinal and sympathetic nerves. The latter, of course, also embraces a multitude of ganglia as well as different ramifications in the form of plexuses and end-plates. For structural and functional reasons the nervous system is commonly divided into a cerebrospinal system and a sympathetic or autonomic system. The former embraces the cerebrum, cerebellum, basal ganglia, medulla, spinal cord, and the cranial and spinal nerves, while the latter includes the different sympathetic and parasympathetic ganglia throughout the body and the nerves connecting these ganglia with the cerebrospinal system. This division is based upon:

(a) *Anatomical grounds*, in that the gross arrangement of the sympathetic system is very different from that of the cerebrospinal, consisting as we shall see later, of a chain of ganglia, which begins above with the superior and inferior cervical, and the superior, middle and inferior thoracic, and ends below with the solar, and the pelvic ganglia. In many places the fibers emerging from these stations, ramify very extensively, and form complex networks, or plexuses.

(b) *Histological grounds*, in that the sympathetic nerve fibers are non-medulated and connect with cells-bodies possessing a very characteristic shape.

(c) *Chemical grounds*, in that the mass of the sympathetic neurones seems to be made up of neuroplasm which is somewhat different from that constituting the cerebrospinal neurones.

(d) *Functional grounds*, in that the life processes regulated by the sympathetic system remain for the most part subconscious. For this reason, sympathetic reactions are very largely non-volitional and reflex in their nature.

The Structural Unit of the Nervous System.—In conformity with other tissues, nervous tissue is composed of two types of cells which may be characterized as true and accessory. The former are called neurons and constitute the functional element of this tissue, while the latter are used for the supporting framework composed of endyma and neuroglia or glia cells. It is true, however, that these cells are indispensable to one another, *i.e.*, one cannot in all probability exist

without the other, but looked at in a general way, it is the neuron which attracts our attention most, because it is more directly concerned with nervous processes. In the terminology of Waldeyer,¹ the neuron or nerve-cell is the histological unit of the nervous system, and as such includes the cell-body as well as its protoplasmic processes, namely, the dendrites, axis cylinder, arborizations and collaterals. Looked at in this way, the nervous system consists of enormous numbers of neurons² supported by glia cells and enveloped here and there by protective membranes, such as the dura mater, arachnoid and pia mater. This constitutes the "neuron concept" of the nervous system. We shall see later on that the structural independence thus granted to the neuron, is associated with an unmistakable physiological distinctiveness.

FIG. 274.—NORMAL ANTERIOR HORN CELL SHOWING THE NISSL GRANULES. (Warrington.)
a, The Axon.

The External Characteristics of the Neuron.—Neurons are cells modified to suit a particular purpose, namely, that of generating and conducting nerve impulses. They are in reality neuroplasmic fibers possessing an accumulation of cytoplasm

at one point of their course in which are embedded a nucleus and nucleolus. In this regard they present the essential details of a cell,

¹ Deutsche med. Wochenschr., xvii, 1891, 1244.

² Kölliker objects to this term upon philological grounds without, however, furnishing a more correct or convenient concept.

because they consist of cytoplasm and nuclear material. It stands to reason, however, that their general configuration must be subject to marked variations, because the physiological processes for which they are destined, necessitate an absolute structural adaptation to the conditions existing in different parts of the body. Thus we find that while nerve-cells always present the characteristics of an elongated conductor, they are frequently so highly modified that it becomes difficult to recognize their true nature. Their structural wealth has been brought out more especially in recent years as a result of more advanced methods in fixing and staining.¹

It is now commonly believed that neurons are developed from single embryonic cells which are called neuroblasts (Fig. 275). These precursors are compact neuroplasmic masses, possessing a round or oval shape and containing a well-defined nucleus somewhere near the center of their cytoplasm. In the course of time, these apolar cells become pear-shaped and finally send out a process which renders them unipolar and eventually multipolar in character. This theory of His has been modified in more recent years² by making allowance for the fact that certain fiber paths seem to be developed directly from the neuroblasts, *i.e.*, the latter may lose their cellular character entirely and be converted solely into axons. Thus, a number of neuroblasts may be joined together in such a way that a conducting path is produced which is then united with other neuroblasts which have given rise to cell-bodies.

FIG. 275.—GROWING NEUROBLASTS.
A, Silver method of Cajal; B, Golgi's method. (Cajal.)

As has been stated above, the mature neurons present such a wealth of structure that it is impossible to classify them satisfactorily. Many of them, however, present a very characteristic appearance, enabling us to recognize them immediately. Cells of this type are the large pyramidal cells of the motor area of the cerebral cortex, the bipolar cells of the sensory ganglia, the fan-shaped cells of Purkinje of the cerebellum, and others. At all events, any attempt at classification must take cognizance of the shape and size of the cell-body and of the number, size, and manner of branching of the processes—axis cylinder and dendrites alike. The shape and size of the cell-body vary considerably. In the cerebral cortex,

¹ Among the investigators who have greatly enhanced our knowledge in this regard, might be mentioned Ehrlich (*Deutsche med. Wochenschr.*, xii, 1886, 49), Apathy (*Proc. Intern. Zool. Congress, Cambridge, 1898*), Golgi (*Arch. fisiol.*, iv, 1897), Nissl (*Die Neuronenlehre, etc.*, Jena, 1903), and Ramon Y. Cajal (*Hist. de Système Nerveux*, Paris, 1909).

² Baglioni, *Zur Analyse der Reflexfunktion*, Wiesbaden, 1906.

for example, we find enormous numbers of small and large pyramidal cells, while those constituting the spinal ganglia, are spherical, and those forming the ventral horn of the gray matter of the cord, rather square irregular. Very typical flask-shaped cells are found in the cerebellum. Many of these cell-bodies are visible to the naked eye, for example, those of the cells of Purkinje (Fig. 276) and those situated in the anterior horns of the gray matter of the cord (150μ). Others, again, are extremely small, measuring only from $4-9\mu$ in diameter.

The large pyramidal cells in the cerebral cortex (Fig. 277) measure from $20-30\mu$ and the small ones from $10-12\mu$ in diameter. Among the smallest are those composing the olfactory bulb, and those forming parts of the cerebellum. Neither are we in a position to give definite measurements regarding the length of the neuron as a whole, because the distances which the different nerve paths must cover, vary

FIG. 276.—PURKINJE CELL FROM HUMAN CEREBELLUM.
Golgi's method of staining. (Stöhr.)

very greatly. It is said, however, that they may attain a length of 1.0 m., bridging the distance between the motor area of the cerebrum and the lumbar region of the spinal cord, or the distance between the latter and the effectors in the foot. On the afferent side, they do not attain so great a length, because the sensory paths are usually beset with a greater number of relay stations. It is also of interest to note that the volume of the axons of these cells greatly exceeds that of the cell-bodies. In large motor cells, for example, the axis cylinder plus its enveloping sheath, possesses a volume 1500 times greater than that of the cell-body. Golgi¹ recognizes three types of cells, namely:

Type 1.—The dendrites are short and ramify in close proximity to the cell-body. Broad and thick at their origin, they gradually become thinner as they divide in an

¹ Boll. d. Societa Med. Chir. di Pavia, 1898-1899.

antler-like manner into their finest terminals. One of the dendrites generally reaches farther into the surrounding tissue than the others. These cells possess a single long axon and serve, therefore, the purpose of conveying impulses over a long distance. In most instances, the axon finally leaves the central system and becomes a nerve fiber, terminating eventually in an end-organ. Its collaterals also break up in arborizations. Cells of this kind are the motor neurons, found in

FIG. 277.—A, B, C, AND D, PYRAMIDAL CELLS FROM THE MOTOR AREA OF MAN.

a, b, Spaces which are filled with tigroid bodies; *c*, pigment; *e*, nuclei of glia tissue; *f*, base of a dendrite; *g, h*, basal portion of axons. (Cajal.)

the cortex of the cerebrum, the anterior horn cells of the spinal cord, and the cells of Purkinje of the cerebellum. Cells of this kind we are prone to picture to ourselves when describing a neuron.

Type 2.—This cell bears the same characteristics as that of the first type, but its axon is short. These neurons, therefore, must serve the purpose of conveying

impulses from place to place within the realm of a single center. For this reason, they generally remain confined to the central nervous system and serve chiefly as intermediate conductors. This deduction seems the more correct, because their axon usually splits into several branches within the gray matter, thus tending to associate its different areas. The first and second types of Golgi cells are, of course, multipolar in character.

Type 3.—This cell is typically represented by the neurons forming the ganglia upon the posterior root of the spinal cord and the ganglia occurring in the course of the sensory branches of the cranial nerves. In lower forms (fish) and also in the mammalian embryo, the cells of the spinal root ganglion possess two processes which leave at opposite poles of the cell-body, and are, therefore, bipolar. In the adult mammal, however, a union has been effected between them so that they now arise as one (Fig. 278). The process passes away from the cell-body but soon di-

FIG. 278.—UNIPOLAR CELLS OF THE GASSERIAN GANGLION.
At *a* is shown the glomerulus formation of the axon. (*Cajal.*)

vides into two, one of which extends into the posterior realm of the cord and the other outward to the corresponding receptors. This peculiar distribution gives rise to a unipolar cell with a T-shaped process, the branches of which become medullated and serve as long conducting fibers. It is questionable whether the impulses conveyed inward from the distant receptor, must first of all enter the cell-body proper before they can be transferred to the central branch. In fact, one of the points regarding the fibrillar theory to be discussed later, is that the cell-body is not necessary for conduction. It may be removed without disturbing the passage of these afferent impulses, and hence, it must be concluded that the dendrite-like distal branch is in direct functional relation with the axon-like central branch.

The Internal Characteristics of the Neuron.¹—The maturing of the nerve-cell necessitates several changes. First, we have the establishment of the polarity of the cell, *i.e.*, the neuroblast sends out an axon, which is soon followed by the formation of dendrites. In some cases, these processes then become medullated or are enveloped solely by neurolemma; or both. While these alterations in

FIG. 279.—CELL FROM THE ANTERIOR HORN OF THE SPINAL CORD OF A RABBIT, SHOWING NISSE'S BODIES.

Ax, Axon; *D*, dendrite; *K*, nucleus; *N*, nucleolus. (*Klopsch.*)

the configuration of the neuron are being completed, the cytoplasm of the cell-body becomes more highly differentiated, presenting finally the following details:

(1) A well marked nucleus and nucleolus surrounded by a relatively thick layer of cytoplasm; (2) flake-like masses of a complex protein substance chemically

¹ Nerve-cells were first recognized by Ehrenberg, in 1833, in the spinal ganglia of the frog. In 1838, Remak established the fact that nerve fibers are prolongations of the cell-bodies. This observation was made upon the sympathetic fibers of invertebrates. It was found to hold true in mammals by Helmholtz and Hanover (1842). In 1863 the observations of Deiters were published which showed that the cells of the central nervous system possess two kinds of processes, namely, protoplasmic prolongations and a real fiber process. Gerlach (1871), Golgi (1873) and Ramon Y. Cajal (1888), furnished additional data regarding the structure of the neuron.

allied to chromatin which are scattered through the cytoplasm and also extend into the larger dendrites but not into the axon. They are generally designated as Nissl's granules or tigroid bodies; (3) strands of denser protoplasm which traverse the cytoplasm in all directions making connections between the different processes of the neuron. They do not invade the nuclear substance. These so-called fibrillæ are said to be continuous with the fibrillæ composing the axis-cylinder, and are regarded as the specific conducting element of the neuron.

To be sure, these characteristics are not shown by all nerve-cells, because some of them possess very small amounts of cytoplasm; while others appear to be composed solely of nuclear material. Nissl¹

FIG. 280.—NORMAL NERVE CELL FROM THE LOBUS ELECTRICUS OF THE TORPEDO. (Garten.)

who has made an exact study of the structural details of the different nerve-cells, divides them into:

1. **Somachrome Cells.**—The cytoplasm surrounding the nucleus, exhibits a distinct structure, showing thereby that it possesses a decided functional importance. By far the largest number of nerve cells belong to this group. They may be subdivided further in accordance with the staining qualities of their cytoplasm.²

2. **Cytochrome Cells.**—Their cell-bodies are poorly developed, so that they seem to be composed of naked nuclei. Cells of this kind are present in the substantia gelatinosa of Rolando and in the granular layer of the cerebellum and olfactory lobe.

¹ Allg. Zeitschr. für Psychiatrie, liv, 1897, 101.

² Barker. The Nervous System, New York, 1899, 121.

CHAPTER XLVI

THE FUNCTIONAL ARRANGEMENT OF THE NERVOUS SYSTEM

The Neuron Doctrine.—While the histological individuality of the neuron has been founded upon the work of many investigators, it was left to Waldeyer¹ to correlate the facts in such a way that clearness was finally brought into the chaos of nervous elements and their function (1891). In accordance with the views of this investigator, the neurons are to be regarded as the building stones of the nervous system, and hence, must be dealt with as independent cellular units. This implies that the nervous system is built up of individual neurons which retain a definite structural relationship to one another. They are connected with one another by means of their processes, but this connection is had only by contact and not by confluence.

We have noted that the neuron possesses an embryological distinctiveness in the form of the neuroblast. To this must now be added its specific histological and anatomical appearance and thirdly, also a definite functional independence. The sum total of their individual actions gives rise to the complex of nervous processes as we observe them in the higher animals. This extension of the neuron doctrine to function followed very naturally upon the establishment of the fact that neurons are structural entities. Physiologically, the neuron concept tends to place emphasis upon the cytoplasm and nuclear constituents of the cell-body rather than upon the conducting paths, so that the former must really be considered as the directing element of the whole.

The Fibrillar Hypothesis.—Contrary to Waldeyer and his followers, it is held by Nissl,² Bethe,³ Apathy,⁴ Schenck,⁵ and Pflüger⁶ that the nervous system is made up of conducting strands of neuroplasm which are directly continuous with one another. The element which is thus brought into prominence, consists of the neurofibrils which, as we have just seen, permeate the cytoplasm of the cell-body and go to form the dendritic and axon processes of the neuron. In accordance with this view, the structural and functional unit of the nervous system is formed by the neurofibril. Here and there a number of these fibrils may pursue a common course and form such structures

¹ Deutsche med. Wochenschr., 1891. Also see: v. Leuhossék, *Der feinere Bau des Nervensystemes*, etc., Berlin, 1895; and Verworn, *Das Neuron in Anat. und Physiol.*, Jena, 1900 and *Med. Klinik*, 1908.

² *Die Neuronenlehre und ihre Anhänger*, Jena, 1903.

³ *Allg. Anat. und Physiol. d. Nervensystemes*, Leipzig, 1903.

⁴ *Mitt. der Zool. Station zu Neapel*, xii, 1897.

⁵ *Würzburger Abhandl.*, ii, 1902.

⁶ *Pflüger's Archiv*, cxii, 1906.

as the axons, but naturally, without becoming confluent or losing their functional independence. In other places, they cross and give rise to by-stations upon the general conducting path which is amplified by the deposition of cytoplasm and nuclear material. Very clearly, however, the fibrillar concept lays emphasis upon the conducting element and attaches little importance to the cell-body.

FIG. 281.

FIG. 281.—CELL FROM THE ANTERIOR HORN OF THE SPINAL CORD OF MAN, SHOWING NEUROFIBRILS.

ax, Axon; *lu*, spaces occupied by tigroid material; *x*, fibrillar connections between neighboring dendrites. (*Bethe*.)

FIG. 282.

FIG. 282.—SCHEMATIC REPRESENTATION OF THE NEUROFIBRILLAR CONNECTIONS IN A PYRAMIDAL CELL OF THE CEREBRAL CORTEX. (*Cajal*.)

The fibrillar hypothesis is based upon structural and functional evidence. Thus, it was found that the large ganglion cells frequently display an intricate network such as is shown in Fig. 282. This network was assumed to represent an intracellular ramification of fibrillæ. Bethe, moreover, has shown that in young animals the degenerating peripheral ends of nerve fibers may regenerate without first having

become connected with their cell-bodies. It has also been proved by this investigator that the cell-body is not essential to conduction. This has been demonstrated in *Carcinus mænas* in which the nerve of the second antenna is composed of centrifugal and centripetal fibers and connects with a ganglion the cell-bodies of which are situated somewhat apart from the fiber network or neuropil. On removing the former, it was found that the antenna regained its former tonus very rapidly and that its stimulation gave rise to reflex actions. Obviously, in this case conduction is had even in the absence of the cell-bodies by means of the fibrillar network or neuropil. Steinach¹ has shown that this condition may be duplicated by causing the cell-bodies of the dorsal root ganglion to degenerate or by removing this ganglion in its entirety. Curiously enough, the sensory impulses continue to pour into the spinal cord even in the absence of this ganglion, and hence, it may be inferred that they reach the central end of the posterior root without being required to make station at this point.

Arguments in Favor of the Neuron Doctrine.—Regarded in a very general way, it may be said that nervous processes are of two kinds: namely, generative or central and conductile or peripheral. The former include the automatic production of impulses and psychic activities such as volition, thought, perception, and others. The latter, on the other hand, merely represent the phenomena of conduction accompanying the passage of an impulse through an axon. In perfect harmony with this functional division, the nervous system presents itself as gray matter and white matter; the former constituting the central nuclei and centers of function, and the latter the paths of conduction by means of which these complexes of ganglion cells are connected either with one another or with peripheral effectors and receptors. Physiologically, it is quite impossible to attribute the generation of impulses to the conducting element of the neuron, the fibrillæ. In other words, creative processes can only be referred to the constituents of the gray matter, the cell-bodies. Thus, the different phenomena of consciousness, the automatic activity of the centers, and other processes, can only be produced by the cellular units of the gray matter and not by the fibers alone, and hence, the liberation of nervous energy is distinctly a duty of the cells.

A similar conclusion must be drawn from the time relationship between impulses traversing nerve fibers and impulses passing through nuclei and centers. It is a well-established fact that their journey through nerve fibers requires a much shorter time than their passage through centers. The deduction to be derived from this is that the ganglion cells possess a specific activity which directly affects the nature of the impulse.

Looked at from the standpoint of embryology, the fibrillar concept fails to establish a structural unit, because the axis cylinders of the nerve fibers do not arise from outgrowths of the cell-bodies, but from

¹ Pfüger's Archiv, cxxv, 1908, 239.

individual local cells which eventually coalesce to form the conducting path. In accordance with the neuron concept, the different neuroblasts finally elongate and form their own axons. These changes may be traced without difficulty in neurons which are made to grow outside the body in a medium of lymph.

The histological evidence favors the neuron doctrine in a very decisive manner. In the first place, it has been proved that the "neurofibrillar" network found in the immediate vicinity of ganglion cells (Bethe), is not composed of fibrillæ at all, but constitutes an intricate system of lymphatic channels set aside for the nutrition of the cell-body. In this connection, reference should also be made to the fact that complexes of ganglion cells are always well supplied with blood-vessels and lymphatics, while nerve fibers are not (Köllicker). In addition, it should be mentioned that some ganglion cells are in possession of an internal system of capillaries. A condition of this kind exists in the cells of the medulla of *Lophius picatorius*. Furthermore, the cytoplasm of some nerve cells contains a hemoglobin-like pigment, a fact which suggests an intense metabolism.¹

The neuron doctrine also receives support from certain data pertaining to the metabolism of the nerve cell. Thus, it has been found by Langendorff² that the gray matter readily assumes an acid reaction upon activity and also becomes acid after death. In analogy with the changes occurring in active muscle, it has been assumed that this acidity is due to the production of lactic acid. It has also been stated by Mosso³ that increased mental activity is associated with a rise in the temperature of the brain. Reference should also be made at this time to the fact that a nerve fiber atrophies when separated from its cell-body, and that ganglion cells display very obvious histological changes during growth or when fatigued. Since a more detailed account of these trophic changes will be given in a subsequent paragraph, attention need only be called at this time to the fact that, unlike the cell-bodies, the nerve fibers cannot be fatigued under ordinary conditions and do not betray an intense metabolism. This fact implies that the refractory period of the nerve fiber is shorter than that of the nerve cell. Naturally, the only deduction to be derived from these data is that the ganglion cells are the more active nervous units and that they serve as the generator or supply house of nerve impulses.

Fatigue of Nerve Cells.—The development of the neuroblast into its mature form manifests itself by a deposition of additional cellular material, an increase in the number of its processes, an acquisition of enveloping membranes and a formation of pigment granules within the cytoplasm.⁴ During their mature state, the neurons become

¹ Fritsch, *Archiv für mikr. Anatomie*, xxvii, 1886, 13; Holmgren, *Anat. Hefte*, xv, 1899, and Pewsner-Neufeld, *Anat. Anzeiger*, xxiii, 1903.

² *Zentralbl. der med. Wissensch.*, 1886.

³ *Die Temperatur des Gehirnes*, 1894.

⁴ Vas, *Arch. für mikr. Anatomie*, 1892.

subject to structural variations in consequence of changes in the bodily activities. In old age, certain retrogressive alterations appear which present themselves in the main as a reversal of the processes observed during the growth of the cell. The cytoplasm decreases in volume, the nucleus becomes smaller, the pigment increases and the different processes decrease in number and mass. In fact, in some cases vacuoles develop which finally lead to the complete disappearance of the cell.

A most interesting picture is presented by nerve cells which have been fatigued. Hodge,¹ Mann² and Lugaro³ state that a normal neuron, when stimulated, first increases in size, because its metabolism is augmented thereby. Excessive activity, however, diminishes the amount of its cytoplasm as well as that of its nucleus until the chro-

FIG. 283.—SPINAL GANGLION CELLS FROM ENGLISH SPARROWS, TO SHOW THE DAILY VARIATION IN THE APPEARANCE OF THE CELLS CAUSED BY NORMAL ACTIVITY.

A, Appearance of cells at the end of an active day; B, appearance of cells in the morning after a night's rest. The cytoplasm is filled with clear, lenticular masses, which are much more evident in the rested cells than in those fatigued. (Hodge.)

matic substance has been used up in its entirety. The Nissl's granules gradually lose their conspicuousness and finally disappear altogether. If long continued, the exhaustion of the reserve supply of energy-yielding material manifests itself in a vacuolization of the cytoplasm and a degree of disintegration from which the cell cannot recover. But if the fatigue is not carried beyond a certain normal limit, the chromophil substance is replenished in time. Very similar changes have been observed in the ganglion cells of birds after long continued flight, for example, in the anterior horn cells of the sparrow and in the antennary lobes of bees at the end of an active day. These

¹ Jour. of Morphology, vii, 1892. 95.

² Jour. of Anat. and Physiol., xxix, 1894. 100.

³ Lo sperim. giornale medico. Biol., F2, 1895.

changes belong in the same category as those following the separation of the cell-bodies from their axons, when the central stump and adjoining cell-bodies undergo retrogressive degenerative alterations. We then obtain a turgescence of the cells which is superseded by atrophic changes and chromatolysis.

The fact that the gray substance of the centers has a definite metabolic requirement, is also shown by the grave symptoms which follow almost immediately upon the occlusion of the carotid arteries or upon obstructions to arteries which supply individual centers of the cerebrum. A functional uselessness of those ganglion cells then results which are situated distally to the block. This uselessness is evinced

either by a loss of motion or sensation, or both. A similar condition may be set up very quickly in rabbits by compressing the abdominal aorta (Stenson's experiment). The anemia of the spinal centers resulting from this obstruction, soon leads to a paralysis of the posterior extremities and, peculiarly enough, the motor paralysis precedes the loss of sensation (anesthesia). This dissociation suggests a difference in the resistance of different nervous elements to anemia.

Verworn¹ states that the fatigue of nerve cells may be brought about in two ways, namely, by causing an accumulation of the waste-products or by exhausting the reserve nutritive material of the cell. The former induces fatigue and the latter, the more serious condition of exhaustion. The experiments which are directly concerned with the metabolism of nerve centers, consisted in perfusing the

FIG. 284.—TWO MOTOR CELLS FROM THE LUMBAR CORD OF A DOG.

A, From rested, and B, from fatigued dog; showing the diminution in the size of the cell, the changes in the size and shape of the nucleus and the chromatolysis. (After Mann.)

central nervous system through the aorta with defibrinated blood and saline solution containing varying amounts of oxygen. Thus, if the blood of a frog poisoned with strychnin, was slowly displaced by saline solution free from oxygen, the muscular spasms gradually became less violent and finally disappeared altogether. The subsequent perfusion with thoroughly aerated defibrinated blood, however, soon caused these spasms to reappear with renewed intensity. The same results were obtained with saline solution fully charged with oxygen, while blood serum free from oxygen, prevented the recurrence of the spasms. This observation proves very conclusively that the recuperation is not dependent upon the organic substances, but rather upon the oxygen;

¹ Arch. für Anat. und Physiol., 1900, 385.

moreover, subsequent experiments have shown that the activity of the ganglion cells varies directly with the quantity of oxygen supplied to them. Hence, their power of oxidation can no longer be doubted.

It has been established that prolonged muscular exercise gives rise to fatigue substances, consisting of carbon dioxid, lactic acid and monopotassium phosphate.¹ In analogy with this observation, Dolly² recognizes a "fatigue of depression" throughout the body, which results in consequence of the production of toxic substances, and a "fatigue of excitation" which follows the excessive consumption of nervous material. Thus, it is a common experience that excessive muscular fatigue reduces our mental efficiency, while conversely, mental fatigue weakens our muscular power and other bodily functions. It is argued further that the highly organized centers are more susceptible to fatigue than the ordinary reflex centers, because mental work produces symptoms of fatigue with much greater ease than muscular exercise. This is especially true of young children who "go stale" very quickly unless their mental training is properly balanced by rest and play. But while we may feel justified in assuming that ganglion cells give rise to fatigue substances, we have not succeeded as yet in isolating these bodies, the only possible exception being carbon dioxid. Winterstein³ has shown that the administration of this gas produces an exhaustion of the nerve cells within a very short time.

The Refractory Period of the Nerve Cell.—It will be recalled that cardiac muscle is impervious to stimuli during systole but gradually becomes more irritable as the end of the diastolic period is reached.⁴ Systole is the period during which the contractile substance is used up, and diastole the period during which it is again acquired. This type of protoplasm, therefore, is not in a condition to receive stimuli so long as those internal reactions are being promulgated which give rise to its contraction. It again becomes receptive during its recuperative period, *i.e.*, during the diastole and pause. In a similar way, it is held that nerve tissue undergoes catabolic and anabolic changes, and hence, a sufficient time must always be allowed to elapse between two successive stimuli, otherwise the material will not be at hand with which to produce the subsequent reaction. Thus, if the successive stimuli are sent into nerve tissue with an increasing rapidity, a point will eventually be reached when no reaction can result. The stimuli then become ineffective, because not enough time has been allowed for the renewal of that material which has been used up during the

¹ The formation of the so-called muscle toxins has been denied by Lee (Proc. Soc. Exp. Med. and Biology, 1917).

² Intern. Monatsschrift für Anat. und Physiol., xxxi, 1914, 35.

³ Zeitschr. für allg. Physiol., vi, 1906, 315.

⁴ Discovered by Marey, (Compt. rend., 1891) and applied to nerve tissue by Broca and Richet (Compt. rend., 1897). These investigators found that the cortical cells are unirritable for some time after the cessation of the muscular spasms, such as occur in chorea and epilepsy.

preceding period of activity. This interval during which the irritability is at low ebb, constitutes the refractory period.

In the case of nerve fibers, the period of refraction is extremely brief, in spite of the fact that they undergo metabolic changes. It amounts to only 0.002–0.006 sec. Their extremely rapid power of recuperation is dependent upon their great affinity for oxygen. It is possible, however, to render this period more evident by lessening the amount of the available oxygen which can be done most easily by surrounding the nerve fiber with some inert gas or narcotizing agent.¹ Cell-bodies behave very similarly, but as their metabolic requirements are much greater than those of the nerve fibers, their refractory period is also more clearly marked. Thus, it has been found that a refractory period of 0.006 sec. for the nerve fibers of the frog corresponds to a refractory period of 0.1 sec. for the ganglion cells of the same animal. This time may be varied by altering the irritability of the cell, either by lessening the amount of the available oxygen or by narcosis.

As the cell-bodies of different groups of neurons are destined to perform different functions, it may be conjectured that their anabolic requirements are subject to considerable variations. Hence, although their refractory period is much longer than that of the nerve fiber, the value of 0.1 sec. must vary somewhat in accordance with the type of cell under consideration. It has also been suggested that the refractory period acts as a check upon those impulses which ganglion cells discharge automatically. It is a well-known fact that the different motor organs, such as muscle tissue and glandular tissue, are constantly kept in a condition of tonus in consequence of an outpouring of subminimal impulses by their respective centers. These impulses are said to be generated at the rate of about 10 in a second. Obviously, as the refractory period amounts to 0.1 sec., they could not be repeated at shorter intervals. Nor could they recur at longer intervals, because the excessive rise in irritability would eventually cause them to be discharged irrespective of any stimulation. It is believed that some ganglion cells discharge their impulses even more rapidly than 10 in a second, namely, 40–100 in a second, but a mere difference in rate does not destroy the principle involved in this process of self-regulation, because the refractory period must necessarily become the shorter, the greater the rate of discharge. At no time, however, could it equal the refractory period of nerve fibers.

Summation of Stimuli in Nerve Cells.—The phenomenon of summation is well illustrated by the summation of the contractions of skeletal muscle. If a number of stimuli of the same intensity are passed into muscle tissue at brief intervals, the resulting contractions are added to one another until the total reaction displays a very much greater amplitude than that of the single contractions. A strength of stimulus may also be employed which does not give rise to a reaction, while two or three stimuli of this intensity applied in rapid succession,

¹ Fröhlich, *Zeitschr. für allg. Physiol.*, iii, 1904, 148.

produce a reaction. This phenomenon constitutes the summation of subminimal stimuli. It should be remembered, however, that we are not dealing in this case with a storage or ordinary addition of individual stimuli, but with a state of increased sensitiveness of the living substance. In other words, the first stimulus, although subminimal in character, gives rise to certain changes in the cell which render it more susceptible to the succeeding stimulus. This is really a general experience, because certain reactions may be elicited with much greater promptness by a succession of moderate stimuli than by a single stimulus of great intensity. This is especially true of the stimulation of the cerebral cortex and other complexes of nerve cells mediating reflex actions.

Setschenow¹ has proved that nerve fibers and ganglion cells behave very differently toward stimuli. Thus, it is conceded that the state of excitation in nerve fibers does not outlast the stimulus for any considerable length of time, while nerve cells retain a state of greater irritability even after slight stimuli and show, therefore, a greater responsiveness to succeeding stimuli. We make use of this fact in a practical way in eliciting reactions in the realm of the sympathetic system and in testing the different reflexes for purposes of diagnosis. Thus, a number of light taps upon the patellar ligament often result in a positive reaction when a single strong one does not. It has also been observed that long-continued pressure is at times more effective than a single mechanical stimulus of much greater intensity. The same is true of the stimuli elicited by stroking the surface of the body (tickling) and of the light, sound and chemical impacts imparted respectively to our retinae, organs of Corti, taste-buds and olfactory cells.

Facilitation or "Bahnung."—Most closely allied to this phenomenon is the so-called stair-case contraction or "Treppe" of striated and cardiac muscle tissue. It will be remembered that if these tissues are rendered more sensitive either by exposing them to subminimal stimuli or by the administration of fatigue substances, their contractions gradually increase and remain large until this state of hyper-susceptibility has been terminated. It should be noticed, therefore, that the "Treppe" is not caused by an increased intensity of stimulation but by an augmentation of the contractile power of the muscle substance. A similar change takes place in nerve tissue when made to perform the same task a number of times in succession. An impulse which is made to pass through a certain set of neurons a great many times, gradually breaks down the resistance in this path so that the latter becomes more particularly adapted to it. This "Bahnung" is largely a matter of the cell-bodies,² because, as we have just seen, the resistance in the centers is infinitely greater than that met with

¹ Über die elektr. Reizung der sens. Rückenmarksnerven des Frosches, Graz, 1868; also: Biedermann, Pflüger's Archiv, lxxx, 1900, 451.

² Exner, Pflüger's Archiv, xxviii, 1882, 487.

along the fiber path. The repetition of impulses, therefore, leads to the formation of open paths, and herein lies the cause of facilitation which in turn gives rise to the formation of habits constituting the neural basis of memory.

Inhibition.—It must be clear that afferent impulses can produce their characteristic reactions only if the neurons over which they pass, do not simultaneously conduct other impulses. Stated differently, the primary impulse must have a perfectly clear path before it, otherwise a conflict will arise between them which must finally lead to the obliteration of one or the other of these impulses. Only the more effective of them will succeed in eliciting a reaction. It is commonly believed that this inhibition and elimination of impulses occurs in the centers and not in the fiber paths, because the function of the central cells consumes time and energy so that they cannot do more than attend to a single activity.

Inhibitory phenomena are explained in two ways, namely, by assuming a paralysis of the assimilative¹ or a paralysis of the dissimilative processes. In accordance with the latter hypothesis, which seems to be the more acceptable, all nervous processes are considered as excitations of dissimilative changes and hence, inhibitions must result whenever this dissimilation following upon the reception of an impulse, is stopped. Clearly, therefore, the chief factor in inhibition seems to be an attenuation of the refractory condition of the nerve cell towards secondary impulses.²

CHAPTER XLVII

THE FUNCTIONAL UNIT OF THE NERVOUS SYSTEM

The Reflex Concept.—In the same manner as the complex masses of nervous tissue may be reduced to a single unit, designated as the neuron, so may all nervous actions be reduced to a simple action, known as a reflex. In the same way as the neuron forms the building stone of the nervous system, so does the reflex constitute the functional basis of all nervous processes. To be sure, there are many organisms in existence which are not in possession of a nervous system nor even of nervous elements, but which nevertheless react in a manner that, relatively speaking, cannot be said to be inferior to the power of reaction of the higher forms. But as these forms are absolutely devoid of nervous tissue, their actions cannot be said to be reflex in

¹ Gaskell, *Jour. of Physiol.*, vii, 1885; also: Meltzer, *New York Med. Jour.*, 1899.

² Verworn, *Archiv für Physiol.*, Suppl., 1900, and *Zeitschr. für allg. Physiol.*, vi, 1907.

their nature. If an ameba retracts its pseudopodia or if a rhizopod sends out its protoplasmic filaments into the surrounding medium, stimulations of some sort must have taken place directly preceding these responses. But as these excitations have resulted in living substance which is free from nervous elements, the reactions, although just as complex as many of those exhibited by the higher animals, can only be said to be reflex-like in their character.

The other group of organisms, embracing those possessing nervous elements, shows a gradually increasing complexity in the arrangement of its nervous units and also a steadily increasing complexity in its reactions. The simplest of these are designated as *reflexes* and the most complex, as associated actions or voluntary *reactions*. The dividing line between these processes lies in volition. Thus, we may use the term reaction in a very general way as designating any response to a stimulus, but, more correctly speaking, it should be restricted to that response which is accomplished with the aid of the will. A reaction, therefore, is a volitional action, while a reflex is an action which is not influenced by volition. To summarize, the different actions shown by animals may be divided into reflex-like actions, reflexes and complex reactions. The first of these are had solely with the aid of ordinary protoplasm, while the last two necessitate the presence of that differentiated type of living substance which we call neuroplasm. Furthermore, as long as an action of the latter kind is not influenced by the will, it remains a reflex, but becomes a complex reaction immediately upon the entrance of volition.

The Reflex Circuit.—It need scarcely be emphasized that the present discussion must be restricted very largely to the analysis of the nervous activities of the higher forms and hence, reflex-like actions must be left for later consideration. The phenomena of life have been divided into spontaneous manifestations and manifestations of stimulation. Strictly speaking, however, this classification is incorrect, because life consists in a reaction of living substance to outside influences. Hence, stimulations are always present and a state of absolute spontaneity cannot arise. Stimuli are constantly brought to bear upon organisms and it is their destiny to react toward them in accordance with their structural and functional equipment. Moreover, if we define a stimulus as any extraordinary alteration in the conditions which nature has imposed upon us, we must immediately be struck by the enormous diversity of influences to which we may be subjected. Animals, very naturally, react toward these changes in harmony with the development of their nervous system. The lower forms being constructed along much simpler lines, are essentially reflex animals, for the reason that their psychic activities are lacking and their actions cannot, therefore, be dominated by the will. The higher animals, on the other hand, are reaction-animals, because their psychic life absolutely controls their simple reflex functions.

A reflex is a response to a stimulus executed without the interven-

tion of the will. This definition implies that the impulse generated in the sense-organ, must be conveyed to a center before it can be transferred to the corresponding motor end-organ (Fig. 285). In its simplest form, therefore, the nervous circuit which is necessary for the mediation of a reflex, must consist of two neurons, one of which serves the purpose of conveying the impulse from the sense-organ (*R*) to the center, and the other, from the center (*C*) to the motor organ (*Er*). The first neuron forms the sensory path (*A*) and the second, the motor path (*E*) of this reflex arc or circuit. The terms afferent and centripetal are frequently applied to the ingoing path and the terms efferent and centrifugal to the outgoing path. Furthermore, the sen-

FIG. 285.

FIG. 285.—DIAGRAM ILLUSTRATING THE CONSTRUCTION OF THE REFLEX CIRCUIT.

R, Receptor; *A*, sensory path; *C*, center; *E*, motor path; *Er*, effector.

FIG. 286.

FIG. 286.—DIAGRAM ILLUSTRATING THE CONSTRUCTION OF THE REACTION CIRCUIT (VOLITIONAL RESPONSE).

R, Receptor; *A*, primary sensory path; *C*, reflex center; *A'*, secondary sensory path; *V*, higher center; *E'*, primary motor path; *E*, secondary motor path, *Er*, effector.

soy side of the reflex arc is often designated as the analyzer, while the sensory end-organ is called the receptor and the motor end-organ the effector. Stated in detail, therefore, a reflex circuit is composed of a receptor, a sensory path, a center, a motor path and an effector.

The circuit required for a volitional reaction, differs from the reflex circuit only in the number of neurons which are necessary to convey the impulse into the cerebrum where the psychic faculties (volition) are situated. The impulse is first conveyed from the receptor to the lower (reflex) center and from here by a secondary afferent neuron to the higher center involving volition. Upon its being transferred to the efferent side of the reaction arc, the impulse first attains the lower center and later on the effector.

The Rudimentary Nervous System is a Reflex System.—The neuron, as has been emphasized above, is the structural unit of the nervous

system. Physiologically, however, the neuron attains its greatest importance only when several of them are joined to form reflex circuits, because only then do we obtain the structural basis for the reflex act which constitutes the functional unit of the nervous system. Obviously, if an electric shock is passed directly into muscle tissue, it reacts by giving a contraction. The same result may be obtained by stimulating the nerve innervating this muscle. In either case, it is to be noted that this action does not constitute a reflex, because it is accomplished in a direct manner and not through the intervention of a number of neurons arranged in proper series. In order that the aforesaid muscular contraction may become a true reflex response, it is necessary to bring the stimulus to bear upon some afferent nerve, whence the impulse is transferred to the motor nerve of this muscle.

Clearly, the cells constituting the tissues and organs of the higher forms, behave in the same manner as unicellular organisms. They possess irritability, conductivity and contractility and hence, give rise to motor effects whenever stimulated. If a vorticella is touched, an excitation results which is conducted to the myoids situated in its stalk. A contraction follows which causes the bell-shaped upper portion of this organism to be retracted from the seat of the stimulation. In a similar way, an electrical shock applied to a muscle, gives rise to a wave of excitation which finally leads to general changes within its myoplasm. The function of the nervous system, therefore, is not to impart these elementary properties to organisms, because all living substance is irritable, conductile and contractile. Its real object is to insure a functional correlation between the different cellular units of the body, so that the latter are enabled to react to changes in the environment as one single coördinated whole. It is also true that nervous tissue is peculiarly suited to bring this coöperation about, because the neuroplasm of which it is composed, possesses the properties of irritability and conductivity in an even greater measure than ordinary living substance.

A general survey of the animal kingdom shows that the forms below the coelenterata do not possess definite nervous structures. Their life processes, as far as we know at the present time, are not correlated by cells other than those forming their tissues. In the coelenterata, however, certain cells are found which are particularly sensitive and appear to be set aside for the singular purpose of receiving stimuli from without and of transferring the resulting impulses to other colonies of cells. We find these units in the external strata of the body, *i.e.*, in the epiblast (Fig. 287, A). Their internal poles are drawn out into slender processes which eventually invade the deeper layers (Fig. 287, B and C). Here they are brought into contact with secondary nervous elements which finally connect with the underlying muscle tissue (Fig. 287, D). An arrangement of this kind, representing really the lowest type of nervous system, is found in the jelly-fish. The sensory cells which are situated in among the external lining cells

of the umbrella, lie in relation with a more deeply placed network of fibers in which a number of nerve cells are embedded. Fibers extend from here to the reactive tissue in the innermost layers of the umbrella, tentacles and manubrium. It appears, therefore, that these organisms are already in possession of complete reflex circuits, each of which is composed of a receptor, a sensory path, an intervening neuron forming the center, and an efferent path with its effector. In fact, this differentiation of the nervous elements seems to have progressed quite far, because the sensory cells show certain individual differences which lead us to suspect that some of them are set aside for the reception of mechanical impacts and rays of light, while others seem to be concerned with the position of the organism in space (static sense).

FIG. 287.—DIAGRAM ILLUSTRATING THE EVOLUTION OF THE NERVOUS SYSTEM.

A, Ordinary living cells; B, processes are sent out by some of them which (C) connect with similar processes of more deeply placed nerve cells; D, the latter in turn form connections with the muscle cells, thereby completing the path between the sensory cell and the effector.

It is, of course, quite probable that a more rudimentary arrangement than this will in time be discovered in other forms; so far, however, the one described is the most elementary with which we are acquainted.

The Evolution of the Reflex System into a Reaction System.—While a segmental arrangement of the tissues and organs is quite apparent even in the highest animals, this condition may be studied most advantageously in such forms as the vermes and crustaceæ. The term segmentalism really signifies that the bodies of these animals are made up of a number of smaller units which are capable of leading an independent existence. This is made possible by the fact that each segment is equipped with a digestive, excretory, circulatory and nervous system, so that a structural dissociation may be effected between them without destroying or seriously impairing their life processes.

As far as the nervous system is concerned, we find that the different segments (Fig. 288) contain a centrally placed ganglion (G) from which

fibers extend in all directions to the different tissues of the segment. A stimulus applied to its surface (S), is soon followed by movements or some other motor response (E), and hence, we must conclude that the nervous material allotted to each segment, is arranged in the form of reflex arcs, the centers of which are situated in the ganglion. While a high degree of independency is thus assured to each segment, it must be admitted that the life of the entire animal requires in addition a proper correlation between its different parts. The functions of its segments must be subordinated to the requirements of the whole. This end is accomplished by intermediary neurons (A) which unite the successive ganglia with one another. These association fibers are placed longitudinally to the long axis of the animal and form in this way a conducting channel akin to the spinal cord of the higher forms. It is also to be noted that the head ganglia are especially well developed and exercise a controlling influence over the other ganglia. Eventually these central complexes also become the recipients of impulses from certain sense-organs, such as the eyes, and the receptors for chemical and vibratory impacts. This is of importance, because the movements and general behavior of the animal naturally demand a proper correlation of all these different sensory impressions. It should be emphasized, however, that those animals which are equipped with a nervous system of this kind, are not capable of forming associations. They are, therefore, true reflex animals for the reason that they are not in possession of those complexes of neurons which give rise to psychic activities (cerebrum).

By way of illustration, let us devote a few moments to a consideration of the nervous system of the crayfish (Fig. 289). It consists of thirteen ganglia, six of which are allotted to the abdomen, six to the thorax and one to the head region. As the most anterior of these lies in close relation with the esophagus, it is usually called the supra-esophageal or supramaxillary ganglion (A). The fibers emitted by every one of these ganglia, are distributed to the muscles and the sense-organs of the integument. They are brought into relation with those of the opposite side by intermediate neurons. Connections are also made with the neighboring ganglia by means of commissural fibers. Each ganglion, therefore, is partially divided into two lobes and this bilateralism is also apparent in the path connecting them. The first thoracic or subesophageal ganglion (C) is more highly developed than the others, because it forms the link between the chain of posterior ganglia

FIG. 288.—DIAGRAMMATIC REPRESENTATION OF THE NERVOUS SYSTEM OF A SEGMENTAL ANIMAL.

G^1 , G^2 and G^3 , Ganglia in three successive segments. S^1 , S^2 and S^3 , and E^1 , E^2 and E^3 , the receptors and effectors of those segments forming the end stations of typical reflex circuits; A , association paths uniting the reflex centers of the successive segments.

and the supra-esophageal ganglion. It appears to be made up of several and sends out two commissures (*B*) which encircle the esophagus and eventually unite with the large supra-esophageal ganglion. Besides, it gives origin to ten pairs of nerves which innervate the mandibles, the maxillæ, and the maxillipedes with their branchial appendages. A still greater differentiation is presented by the head ganglion which consists of three pairs of nodular enlargements, namely, the protocerebrum, the deutocerebrum and the tritocerebrum. The optic nerves (*O*) enter the foremost of these, while the middle ones receive fibers from the integument, antennæ and organ of hearing (*R*). The posterior nodules give origin to the nerves innervating the large external antennæ (*D*).

FIG. 289.—
DIAGRAMMATIC
REPRESENTATION
OF THE NERVOUS
SYSTEM OF THE
CRAYFISH.

A, Supraesophageal ganglion; B, commissure; C, subesophageal ganglion; D, first abdominal ganglion; O, optic nerve; R, middle nerve; P, antennary nerve; S, stomatogastric nerve.

An arrangement of this kind constitutes a typical reflex stem, around which, in the higher forms, the association or reaction system is developed. The greatest change is effected anteriorly in the region of the head ganglia, because these bodies are destined to become the recipients of the impulses from the chief sense organs. Eventually, many of these impulses are not permitted to pass directly upon efferent channels, but are first conducted into certain complexes of nerve cells in which they are associated. In this way, each sensory reflex area is finally invested by a sphere of association, the nervous products of which give rise to the psychic life of the animal. This development of the different association centers takes place gradually. The first to make its appearance is the center for smell, because smell is the most primitive sense and many animals, such as the amphibia and reptilia, depend upon it almost exclusively. It need scarcely be emphasized that the development of these association spheres increases the complexity of the nervous system very pronouncedly, because the primitive reflex stem is now materially augmented by the addition of the brain. Quite aside from this structural and functional complexity of the nervous system of the higher animal, it should be noted especially that its reflex life is completely subordinated to the activities of the association centers situated in the more recently formed cerebral hemispheres.

The Joining of the Reflex Circuits.—The structure of the most elementary reflex arc has been fully considered in one of the preceding paragraphs. It consists of a receptor, an afferent path, a center, an efferent path and an effector. Moreover, it is to be noted that, in the lowest forms, these reflex circuits are few in number and retain a marked independency of one another. In the higher animals, on the other hand, they increase greatly in number and become closely linked by intermediary neurons which thus establish a close functional relationship between them. The simple reflex arc (Fig. 290) may be compounded first of all into a reflex chain consisting of several arcs

(B). The impulse producing the primary reflex response is thus enabled to spread and to incite other responses until the so-called chain reflex is obtained. Another way in which these reflex arcs may be arranged is illustrated by Fig. 290, C. Here two effectors are connected

with a single receptor, the efferent paths originating from a common center. These effectors may or may not act in unison; *i.e.* they may be allied or antagonistic in their function. If the former case, the reaction simply becomes more diversified and complex, but continues to present a perfectly co-ordinated character. An antagonistic behavior on their part, however, must lead to a disconcerted reaction which, in most cases, can only be prevented by inhibiting the action of one of the effectors. Conversely, two receptors may be associated with only one effector (*D*). If stimulated simultaneously, the impulses arising in these receptors, will have a tendency to interfere with one another until the more effective of the two finally succeeds in gaining the common path to the effector. It may also happen that these impulses, if

FIG. 290.—DIAGRAM ILLUSTRATING THE JOINING OF REFLEX CIRCUITS.
R, Receptor; *C*, center; *E*, effector.

simultaneously elicited, reinforce one another so that the response becomes much greater than it would have been if only one of them had been received. Reflex arcs may also be combined into the form represented by Fig. 290, *E*. We observe here that the successive circuits are brought into close relation with one another by connecting paths, so that the stimulus applied to one of them may skip either to the same or to neighboring effectors, or both. In this way, much more complicated reflexes may be elicited which, although for the most part allied, may at times assume an antagonistic character.

It will be pointed out in a subsequent paragraph that the spinal cord, in combination with the spinal nerves and those apportioned to the sympathetic system, is especially well adapted for reflex action. In fact, as the cord really consists of a large number of reflex centers

and their connecting paths, it is commonly regarded as one of the chief realms of reflex action. This statement, however, is not meant to convey the idea that the cerebrum and other complexes of the nervous system are composed exclusively of reaction circuits, and are devoid of reflex circuits. Such an assumption could easily be proved to be incorrect, because many of the most common reflexes invade the cerebrum and neighboring parts. For example, if the intensity of the light is increased, the pupil is constricted, or if the cornea is touched, the eyelids are closed. Similarly, we react to sound impressions quite frequently by movements of the head, and to visual impressions by a hyperproduction of saliva and gastric juice. In all these instances, as well as in many others that might still be mentioned, at least a section of the reflex circuit is situated in the realm of the cerebrum and parts immediately adjoining. Nevertheless, these actions are thoroughly reflex in their nature. As additional proof it might be mentioned that a group of reflexes, known as the association reflexes, actually necessitate the formation of distinct sensory concepts, otherwise the motor response invariably fails to develop. This is true, for example, of the act of yawning elicited by observing somebody else yawning, and of the flow of saliva and gastric juice following the sight of attractive food. In all these cases, volition does not play a part and hence, it must be concluded that reflex circuits may be found in all parts of the nervous system and even in the domain of the cerebrum, where they are brought into relation with the processes of consciousness. It is to be noted, however, that the impulses conveyed by them do not lose their reflex character unless dominated finally by volition. Whenever this change takes place, the reflex becomes an associated act or a volitional reaction.

The conditions found in the lower forms are most closely simulated in the sympathetic system, because this system consists of a series of ganglia which are connected with one another by closely interwoven nerve fibers. While these ganglia are generally situated in the immediate vicinity of the structures innervated by them, they may also be placed directly within their substance. If we direct our attention for a moment to the stomach and intestine, we find that these organs may be made to contract and to secrete even outside the body, provided that they are kept under proper conditions of moisture and temperature. They are thus proved to possess a remarkable independency of function which is made possible by the fact that they are amply equipped with reflex circuits which in all probability are contained in the plexuses of Meissner and Auerbach. But even if these organs are left in situ, it is not difficult to divide the bridges connecting them with the cerebrospinal system. In this way, volition may be absolutely excluded from them as well as from all other sympathetic organs. Since their functions are not seriously disturbed thereby, it must be concluded that they are typically reflex in their nature.

Very similar conditions are met with in the spinal cord, the reflex

nature of which may be more clearly portrayed by severing the connections between it and the brain. This end may be attained by a section made either above or below the medulla oblongata. It will be shown later on that an animal of this kind retains all those functions which are ordinarily accomplished with the aid of the cord. These responses, however, need not remain confined to a particular segment of this structure, but may also involve higher or lower spinal centers without losing their reflex character. The reactions of a "spinal cord animal" must necessarily be non-volitional.

When referring to reflex circuits and actions we are accustomed to associate them immediately with the spinal cord. The preceding discussion, however, must have made it clear that they are not exclusively confined to this structure, but may involve almost any part of the nervous system. It seems that the spinal cord is referred to most frequently in this connection, because it is a relatively simple matter to isolate it and to stimulate its nerves. Moreover, the spinal reflexes are perfectly conscript actions and pursue easily recognizable paths.

CHAPTER XLVIII

REFLEX ACTION¹

The Different Types of Effectors and Receptors.—If we adhere to the general definition that a reflex is a non-volitional motor response to a sensory impulse, the very diverse and complex character of these reactions must immediately become evident. On the efferent side, of course, conditions are relatively simple, because the effectors consist of only two structural units, namely, the muscle cell and the gland

¹ The term sympathy or consensus was applied by the ancients to almost all phenomena of life. In 1649, however, Descartes separated from these general reactions all those which did not produce an impression in consciousness and were not subjected to the will. He applied to this class of reactions the term *reflex*, because in analogy to the reflection of light, the sensory impression seemed to be returned in the form of a motor effect. Subsequent to this time, Willis (1664), Astruc (1743), and Unzer (1771) have described various reflexes such as the acts of coughing, sneezing, the closure of the eyelids, the ejaculation of the semen, and others. Their idea, however, seemed to be that these reactions can be brought about with the help of the nerve trunks and do not require a center. Whytt (1751) then proved that this conception is incorrect, because in the frog the destruction of the spinal cord immediately destroys the reflex actions ordinarily elicited with the help of this part of the nervous system. He also described the reflex secretion of the tears and of saliva, and recognized the fact that the latter may also be obtained by psychic stimulation; in other words, he recognized the association reflex. The modern conception of reflex action is based upon the work of M. Hall (1832-33) and Joh. Müller (1833-34).

cell. The former gives rise to motion and the latter to secretion. It must be remembered, however, that the muscle cell presents itself in three forms, giving rise respectively to the striated, non-striated and cardiac tissue, and furthermore, that especially the second type of muscle cell is a constituent of a most perplexing array of structures. Thus, we find it in the iris, ciliary body, stomach, intestines, blood-vessels, ureter, bladder, sexual organs, skin, etc. In all these cases it responds to stimuli by contracting, but the effect produced thereby differs greatly in accordance with the general arrangement of the tissue in which it is embedded. Clearly, the movement shown by the iris, is different in character from that of the contracting stomach or bladder. The same is true of the gland cell. While representing only one type of effector, this cell appears in various forms as a unit of the multitude of the glandular structures present in our body. Its stimulation, therefore, must give rise to secretions of very different appearance and composition. Thus, while it is customary to illustrate reflex action with the help of motion, and especially with that type of it which is caused by striated muscle, it should not be forgotten that the body is also in a position to give a multitude of secretory responses.

The conditions met with on the afferent side of the reflex circuit, betray a much greater diversity of structure and function. The layman commonly states that there are five sense organs present in our body, namely the eyes, ears, nose, tongue and skin. We shall find, however, that these five so-called external senses are augmented by about twenty others which are chiefly concerned with the impressions brought to bear upon internal parts. It appears, therefore, that the two effector units, the muscle and the gland cell, are opposed by more than twenty receptors, every one of which presents very special structural characteristics. Motion or secretion are thus given in answer to sensory impressions received from a relatively great number of diversified receptors.¹

The Reflex Animal.—In studying reflex action, it is customary to make use of a frog, the brain of which has been removed or destroyed by the process of pithing. Obviously, this procedure destroys the "psychic" life of this animal and renders its actions absolutely non-volitional. An animal of this kind, therefore, is incapable of experiencing pain or of receiving any other sensation in consciousness. In the absence of the cerebrum, an afferent impulse must necessarily remain a simple reflex sensation. The removal of the cerebral hemispheres, therefore, serves the purpose of converting the frog into a simple reflex animal.

The reflexes commonly studied subsequent to this procedure, are those occurring in the domain of the spinal cord, *i.e.*, the so-called spinal reflexes. The frog is suspended from a hook passed through its lower maxilla. The sole of the foot is then stimulated either by

¹ A further discussion regarding the structure of receptors will be found upon page 729.

applying the electrodes lightly to its surface or by pinching the skin with a pair of forceps. If more convenient, the foot may be immersed in a weak solution of acetic acid. In either case, the stimulus presently gives rise to a contraction of the muscles of the corresponding leg which results in its withdrawal from the seat of the stimulation. If electrical stimuli are employed, the student should sharply differentiate between the direct effect of the current as evinced by a twisting of the toes, and the reflex effect, consisting in a more general muscular action and the actual withdrawal of the leg. It should also be observed that the stimulus is applied in this case to the tactile receptors of the skin and that the response consists in a seemingly purposeful movement. This reaction is similar to the one occurring in us whenever our integument is suddenly stimulated, say, in a mechanical way. The subsequent contraction of the musculature necessary to perform the protective movements corresponding to this stimulus, is non-volitional, *i.e.*, the response is had without that its character can be changed by the will. In many cases, of course, we obtain a perfect sensory concept of this act, but the sensorium is activated in this instance after the completion of the primary act and cannot, therefore, influence the latter in any way. But if this cutaneous stimulus is first received in consciousness and is there subjected to volition, the resulting response ceases to be a reflex and becomes a complex reaction.

Reflex Time. Reflex Fatigue.—The time elapsing between the moment of the application of the stimulus and the beginning of the response, is known as the reflex time. As is easily observed in the reflex frog, this factor varies with the strength of the stimulus and the irritability of the nervous system. It has been stated above that a series of slight stimuli are more effective than one strong one, and that the best results are obtained if the receptor itself is stimulated and not the afferent path leading from it. Thus, if a tetanic current of very moderate strength is applied to the sole of the foot of the reflex frog, a perfectly definite muscular response is evoked, consisting in a seemingly purposive removal of the foot from the seat of stimulation. There is, of course, no intent present, because this result is wholly dependent upon the general structural arrangement of the leg. If the intensity of the stimulus is now increased, the response follows with the same mechanical precision, but at a somewhat earlier moment. In other words, the reflex time is inversely proportional to the strength of the stimulus. It is also possible to vary the reflex time by altering the receptive power or irritability of the nervous system. Depressive agents, such as the narcotics, lengthen it, while stimulants, such as strychnin, oxygen, warmth, etc., shorten it.

We are thus justified in applying to reflex action such characterizations as "subminimal reflex stimulus," meaning thereby the stimulus which just fails to elicit a reflex response, or "reflex threshold," indicating thereby the stimulus which is just becoming effective. It

is also evident that the repeated elicitation of a certain reflex is very prone to lengthen the reflex time and to lessen its conspicuousness, because the structures participating in this reaction become fatigued. We are thus forced to recognize the condition of "reflex fatigue," and to admit that reflexes also possess a definite "refractory period." This implies that they cannot be elicited at shorter intervals than are required for the anabolic changes in the different elements of the reflex circuit.

In all these cases, the cell-body, rather than the conducting paths, seems to be the deciding factor. It is to be noted, however, that the reflex time includes several elements, namely, the time of conduction of the impulse through the afferent and efferent paths, its passage through the center and lastly, the latent period of the motor organ. Helmholtz¹ has shown that the transfer of the impulses through the gray matter of the spinal cord consumes twelve times as long a time as their passage through the peripheral conducting channels. The total reflex time may thus be regarded as being composed of the "rough" and "reduced" reflex phases. The former includes the time elapsing between the moment of stimulation of the receptor and the onset of the response, and the latter, the time consumed by the processes occurring in the center, *i.e.*, the total time less the time of conduction over the afferent and efferent paths and the length of the latent period of the motor organ. Exner,² for example, states that the closure of the eyelids upon stimulation of the cornea (corneal reflex) occupies 0.0578–0.0662 second. As the conduction requires in this case, 0.0107 second, the central transfer must consume 0.0471–0.0555 second. Listing and Vintschgau³ estimate the time of the reaction of the iris to varying intensities of light (light reflex) at 0.3–0.4 second. The reactions accomplished with the aid of smooth muscle, are much slower, a fact which is in keeping with the lesser irritability of this tissue as well as of the nervous elements innervating it. This is especially true of the sympathetic system.

Spreading or Crossing of Reflexes.—If the stimulus applied to the foot of a reflex frog, is of slight intensity, the leg is withdrawn in a gradual and easy manner, while if the stimulus is severe, the leg is jerked up, and besides, the muscular contractions do not remain confined to this limb, but spread to the muscles on the opposite side and possibly also to those of the trunk and forelegs. This result indicates that the primary afferent impulse has been transferred to other reflex circuits, or better, that the primary reflex has led to an activation of those reflex circuits which are in functional relation with the one involved first. In order to allow this spreading to take place, certain intermediary neurons must be present, the purpose of which is to

¹ Prot. der Akad. d. Wissensch., Berlin, 1845; also Fano, Arch. ital. de biol., xxxix, 1903, 85.

² Pflüger's Archiv, viii, 1874, 526.

³ Ibid., xxvi, 1881, 324.

conduct the impulses up or down in the spinal cord. This arrangement is clearly indicated in Figs. 291, 292 and 293. The first two illustrate the conduction paths required for a simple reflex in which a single posterior extremity is involved. In

FIG. 291.

FIG. 292.

FIG. 291.—SCHEMA TO ILLUSTRATE SIMPLE REFLEX CONDUCTION IN THE SPINAL CORD. A, The sensory impulse is immediately transferred to the motor path E.

FIG. 292.—SCHEMA TO SHOW SIMPLE REFLEX CONDUCTION IN THE SPINAL CORD.

A, The sensory impulse is transferred in the anterior horn to the motor neuron E.

this case, the impulse arriving by way of the sensory neuron, is immediately transferred to the motor neuron in the anterior horn of the gray matter, and from here to the corresponding effector. Figure 293 shows how intermediary neurons enable the impulse to attain higher or lower levels of the spinal cord, where connections are formed with the motor cells and effectors situated at a more remote distance from the primary circuit. The spreading of a reflex to adjoining arcs may be demonstrated in various ways. If the leg of a frog to which a stimulus has been applied, is firmly held in place so that the motor effects cannot fully develop on this side, the primary action eventually spreads to the muscles of the opposite limb as well as those of the trunk and forelimbs. It is also possible to elicit this phenomenon by stimulating the central end of the divided sciatic nerve of one side. As this section renders the muscles of the same side functionally useless, the afferent impulses generated at the seat of the stimulation, find their way into the motor paths of the opposite leg as well as into those of the trunk and forelimbs.

FIG. 293.—SCHEMA TO ILLUSTRATE REFLEX SPREADING IN THE SPINAL CORD.

A, The sensory impulse is transferred to an intermediary neuron *j* which conveys it to higher and lower motor paths E.

In general, it may be said that reflexes may be made to spread (a)

by increasing the intensity of the stimulus, and (b) by heightening the irritability of the nervous structures. The latter effect may be evoked by any agent possessing a stimulating action upon the nervous system, such as a weak solution of the sulphate of strychnin. If this drug is injected under the skin covering the dorsal aspect of the frog, its gradual absorption finally leads to an increased susceptibility to stimuli which is clearly betrayed by the extensive and intense muscular spasms resulting in consequence of even the slightest possible tactile or electrical stimulus. The mere touch of the plate upon which the strychninized frog has been placed or a current of air blown across the surface of its body, now suffices to throw every muscle into a state of prolonged contraction. The explanation usually given for this effect is that the strychnin lessens the resistance to conduction. It is said to accomplish this end by increasing the continuity in the synapses, *i.e.*, it is supposed to bring the axon and dendritic terminals into closer relationship so that the impulses are enabled to spread more readily from neuron to neuron.

Inhibition of Reflexes.—This phenomenon consists in a lessening and final abolition of the motor response following the application of a stimulus. It is commonly believed that this depression is brought about by a blocking of the reflexes in their respective centers. The impulses which accomplish this end are derived from different sources, namely, (a) from the faculty of volition in the cerebral hemispheres, (b) from higher reflex centers situated in the midbrain and hindbrain, (c) from peripheral nerves, and (d) from a lessening of the irritability of the nervous system as a whole.

Cerebral Inhibition.—It is a matter of common experience that reflexes may be suppressed by volitional efforts. While, under ordinary conditions, a touch upon the cornea gives rise to a quick closure of the eyelids, special efforts may be made to overcome this stimulus. In a similar manner, we may counteract the stimulus which ordinarily gives rise to the act of coughing or sneezing. It seems, however, that this cerebral inhibition necessitates two conditions, namely, that the excitation be of moderate intensity, and that the reflex which we endeavor to suppress, be in functional relation with volition. It must be evident that a strong excitation must eventually overcome even very powerful counter efforts and furthermore, as a large number of our reactions are not under the guidance of the will at any time, it must be clear that volitional efforts cannot be brought to bear upon them. This exception applies especially to the motor end-organs consisting of smooth muscle tissue and situated in the domain of the sympathetic system. Thus, we are quite unable to inhibit vasomotor and pilomotor reactions or to vary the size of our pupils in antagonism to the stimulations received from the retina. This exception is also apparent in the case of several striated muscles, because we are unable to influence the cremasteric reflex and to counteract the contraction of the musc. bulbocavernosus.

The inhibitory power of the cerebral cortex upon reflex action is well illustrated by the changes in the "croaking reflex" of the frog occurring in consequence of the removal of the hemispheres. Under normal conditions, this act necessitates a certain psychic activity.¹ It is dependent upon certain elementary associations

¹ Goltz, Beitrag zur Lehre von den Funktionen der Nervenzentren des Frosches, Berlin, 1863.

and is executed volitionally. The removal of the cerebrum converts this previously complex reaction into a pure reflex, as may be gathered from the fact that the decerebrated frog produces this sound at any time in consequence of such cutaneous stimulations as the stroking of the skin of the dorsum or the application of a gentle pressure to the sides of the abdomen. Moreover, this reflex may be repeated almost any number of times until reflex-fatigue causes it to cease. Another experiment illustrating cerebral inhibition of reflexes, is the following: When the female frog deposits its eggs, the male endeavors as a rule to aid its mate by firmly clasping her abdomen with his fore limbs. This reaction on the part of the male may be converted into a reflex by removing the cerebrum, as is evinced by the fact that the decerebrated male may be made to clasp objects of any kind by simply bringing them in contact with the ventral aspect of his thorax. In fact, it is possible to produce this reflex even in the absence of all parts excepting the thorax and the two forelimbs. In the higher animals, the removal of the cerebrum distinctly shortens the time of the spinal reflexes and leads to the appearance of certain reflexes which under normal conditions are scarcely perceptible. Such acts as licking, scratching, growling, etc., then assume a clear reflex character, because the influence of volition has been permanently removed from them.

Inhibition by the Midbrain.—It has been assumed that reflex action is regulated by a higher center which, in accordance with Setschenow,¹ is located in the mid-brain, *i.e.*, in the optic lobes of such animals as the amphibia and reptilia. This conclusion is based upon the observation that the removal of this part of the nervous system shortens the time of the spinal reflexes and renders them more vivid. The opposite effect may be produced by stimulating these bodies while eliciting any one of the spinal reflexes. The evidence, however, seems to be against the existence of specific inhibitory centers for reflex action. Instead, it is generally assumed that the optic lobes (*corpora quadrigemina*) and other bodies, are enabled to unfold this faculty in consequence of their connection with the chief conducting channels passing to and from the cerebral hemispheres. In the lower vertebrates, they are of even greater importance, because they give origin to the optic nerves. It is only natural to suppose that the sensory impressions derived from this source must tend to hinder simple reflex action even in the absence of special inhibitory centers. It seems, therefore, that this form of inhibition may be most easily explained upon the basis of a central interference of different afferent impulses with one another.

Inhibition by Other Afferent Impulses.—It is a well recognized fact that reflexes may be inhibited by simultaneous afferent impulses. The act of sneezing may be suppressed by exerting a gentle pressure upon the upper lip or by rubbing the nose. Quite similarly, a mechanical stimulus to the skin may be rendered abortive by a second stimulus applied elsewhere to the integument. Thus, it may easily be shown that the reflex caused by stimulating the sole of the frog's foot, may be completely inhibited by the simultaneous excitation of the central end of the opposite sciatic nerve. In the absence of distinct inhibitory reflex centers and nerves, these results can only be explained upon the basis of an interference of impulses, resulting, as has been more fully discussed above, in the ganglion cells of the reflex circuit involved in this particular act. In consequence of the refraction of the cell, one of these impulses is rendered ineffective.

Strong and continued stimulation of sensory nerves eventually leads to a depression and complete abolition of almost all reflexes. This condition is known as "shock," and if the immediate cause of this depression is located in the realm of the spinal cord, as spinal shock.

*Shock.*²—A person in shock is usually found in a state of complete muscular

¹Physiol. Studien über die Hemmungsmechanismen, etc., Berlin, 1863. Meltzer, The rôle of inhibition in normal and pathological phenomena of life, Med. Record, 1902.

²Short, Lancet, 1914, and Wiggers, Am. Jour. Med. Sciences, clii, 1917, 666.

relaxation and if movements are made, they are feeble and irregular. The face is pale and drawn, the pupils dilated, sweating is often profuse, the reflexes are slight, consciousness is usually present but there is a diminished sensibility and mental activity. The respirations are feeble, irregular and sighing. The pulse is small, frequent and dicrotic, owing to the low blood pressure. The skin is cold and the temperature subnormal. The theories which have been brought forth in explanation of this phenomenon, may be grouped as follows:

(a) Exhaustion of the vasomotor mechanism by a depression of the activities of the center. This theory is not satisfactory because while shock commonly induces a fall in blood pressure, the vasomotor center is not exhausted and the blood-vessels may be constricted; moreover, the heart is not seriously affected, although its output is small.

(b) Acapnia, or deficiency in CO_2 , removes a most important stimulus from different nerve centers. The breathing becomes shallow and occasional, the blood-pressure falls and the heart beats more quickly. The objections to this theory are many, chief among which is that shock should then be prevented by artificially supplying CO_2 , which is not the case.

(c) Oligemia, or too little blood, acts by reducing the blood pressure, but allows the cardiac and vasomotor centers to continue their activities. Gravity shock may be classified under this heading, because it is caused by a stagnation of blood in the splanchnic blood-vessels and consequent inadequate filling of the heart. Thus, when a rabbit with a large pendulous abdomen is held vertically with the head up for any length of time, it frequently passes into the condition of shock and may die within 20 to 30 minutes.

(d) Exhaustion of adrenin, brought about by an initial outpouring of excessive amounts of adrenin in consequence of sensory stimulation. This finally leads to its exhaustion.

(e) Inhibition of the activity of the nuclei of the spinal cord and midbrain.¹ When such an inhibition takes place, the function of the cord is greatly diminished. Consequently, its constituent nuclei cease sending out those impulses which maintain the tonus of the muscles. The blood pressure falls. Even the respiratory center shares in the paralysis. Eventually a venous engorgement is obtained which makes a proper filling of the heart and arterial channels impossible. Spinal shock, however, possesses a rather local character, because it affects only those parts of the body which lie below the seat of the spinal lesion. Under this heading may be classified the so-called nervous shock or shell shock, as well as the shock accompanying overdoses of anesthetics. In the latter case, however, the reflexes reappear after the discontinuance of the narcosis, while in surgical shock they do not.

Inhibition in Consequence of the Lessening of the Irritability of the Nervous System.—This condition results during sleep and narcosis. The reflexes which are abolished first, are the abdominal, cremasteric and patellar, while those from the sole of the foot and from the nasal mucosa are more resistant. The reflexes which disappear last are the corneal and retinal. For this reason, sleep and narcosis may be employed as a means to determine whether or no an action is a true reflex, because, if it persists during these states of cerebral depression, it must be non-volitional. In infants and children this weakening of the reflexes is less evident than in adults. It need scarcely be mentioned that the intensity of the reflexes may be made to serve as an index of the depth of the narcosis. The reactions usually employed for this purpose are the corneal and pupillar (light) reflexes, the danger line being reached when a mechanical impact upon the cornea very nearly fails to elicit a contraction of the musc. orbicularis palpebrarum and when immediately thereafter the pupils become constricted. A weakening and final inhibition of the reflexes also results in coma and depressions of the nervous system resulting

¹ Pike, Am. Jour. of Physiol., xxx, 1912, 436, and Porter and Mühlberg, *ibid.*, iv, 1900, 334.

from cerebral concussion and the absorption of toxic agents, such as picrotoxin, morphin, quinin, potassium bromid, and others.

Acceleration and Conditioning of Reflexes.—Certain conditions may arise at times which will tend to augment reflex action in such a degree that it becomes difficult to differentiate these responses from those previously described under the heading of spreading of impulses. The causes to which this acceleration may be assigned are twofold. Thus, it may be caused either by an increase in the strength of the stimulus or by a heightened irritability of the nervous tissue. If an irritant is applied to the nasal mucosa of a strength just sufficient to incite merely a slight tendency to sneeze, this primary stimulus may be reinforced by the act of sniffing. Clearly, as this augmentation is dependent upon volition, it must be attained with the help of the cerebrum. We are also in a position to strengthen those reflexes which ordinarily result in consequence of cutaneous impressions, either by the application of cold water or by stimuli involving the optic or auditory mechanism. In a similar manner, the corneal reflex may be accelerated by gently blowing a current of air across the surface of the conjunctiva. On the whole, however, it must be conceded that reflex acceleration cannot be effected so easily as reflex inhibition.

By far the largest number of reflexes are not conditioned. A particular kind of stimulus gives rise to a particular reaction with almost mechanical exactitude. This is true of coughing, sneezing, yawning and other acts with which we are familiar. It is possible, however, to subject these reflexes to other influences so that they assume an elaborated or conditional character.¹ Thus, we are able to incite a flow of saliva quite readily by the introduction of a drop of dilute acetic acid into the mouth of the subject. If this stimulation is repeated a number of times at intervals and if this stimulation is accompanied by a visual impression, such as may be effected by a receptacle filled with colored water, the primary stimulus may be dispensed with in time, because the retinal stimulus alone will then suffice to produce the aforesaid result. While many of our reflexes may be conditioned in one way or another, it is true that this cannot be done without the help of perception. In other words, the conditioned reflexes require training or education. This conversion of a simple reflex into an association reflex, however, does not necessitate the participation of volition; in fact, it precludes this modification for the reason that the reflex would then lose its primitive character and become a reaction.

Classification of Reflexes.—In accordance with their qualitative peculiarities, reflexes are divided into:

(a) *Simple reflexes*, in which a single muscle or glandular unit is involved. As an example of this kind of response might be mentioned the corneal reflex. The afferent arc is formed by the nervi ciliares trigemini and the efferent arc by the

¹ Pawlow, *Livre jubil. du Prof. C. L. Richet*, 1912.

orbicular branches of the facial nerve. The effector is the musc. orbicularis palpebrarum.

(b) *Complex reflexes*, in which several muscles or secretory units are affected, but the response remains perfectly co-ordinated, in spite of the fact that the effector is now more diversified. As an example of this kind of response might be mentioned the patellar reflex. The stimulus is applied to the patellar ligament whence the impulse is transferred to the sciatic center by way of the afferent fibers of this nerve. It attains the muscles upon the anterior aspect of the thigh by way of the efferent fibers of the same nerve (ant. crural nerve).

(c) *Spreading reflexes*, in which a large number of motor organs are involved. Thus, a certain stimulus may lead to the contraction of many muscles far removed from one another. Their action, however, remains co-ordinated.

(d) *Antagonistic reflexes* are made possible by the so-called reciprocal innervation, first described by Sherrington.¹ It frequently happens that the reflex activation of a certain muscle causes at the same time a lessening of the tonus of the corresponding antagonistic muscle. In a similar way, the relaxation of a previously contracted muscle very frequently incites a contraction of the relaxed antagonistic muscle. This phenomenon is most clearly displayed by the flexors and extensors of the arms and legs, and also by the constrictors and dilators of the iris and other reciprocating effectors. It seems, however, that this reciprocity is not dependent upon a paired arrangement of the peripheral nerves, but upon a peculiar adjustment of the motor centers governing the action of these antagonistic muscles.² Apparently, their connection is such that the excitation of one motor cell causes the activity of the other to be inhibited.

(e) *Tonic and Spastic Reflexes*.—The reaction following a certain stimulus is usually prolonged, and lasts much longer than the stimulus. In many cases, in fact, it assumes so continuous a character that it may be characterized as a true reflex spasm. Experimentally, this peculiarity may be imparted to reflexes very easily by the administration of small doses of strychnin or morphin. It is also a frequent symptom of certain pathologic conditions tending to augment the irritability of the nervous system. A not uncommon reflex of this type is the condition known as blepharospasm, a tonic spasm of the eyelids.

(f) *Periodic and Clonic Reflexes*.—In many instances a stimulus may cause a certain response to be repeated a number of times at regular intervals. This is true of the acts of sneezing, coughing, hiccoughing, swallowing, the clattering of the teeth, and trembling. The cremasteric reflex also consists of an often repeated raising and lowering of the testicle. The same is true of the scratching reflex, and of those which may be elicited in decerebrated cats and dogs by tickling the lateral aspect of the abdomen. In many cases, these reactions recur at very brief intervals and assume a prolonged or clonic character. Of especial clinical importance is the ankle clonus, a periodic reflex which may be set up by suddenly flexing the foot and stretching the tendo Achillis. In certain nervous diseases even the patellar reflex may assume a clonic character.

(g) *Alternating reflexes* are commonly produced by an alternating activity of antagonistic groups of muscles. Instead of one reaction, a number of them are obtained in orderly sequence. The rocking back and forth of the head upon the trunk may be cited as an example of this type of reflex. In decerebrated animals certain stimuli produce at times an alternate flexion and extension (kicking) of the two posterior extremities.

(h) *Association or Perception Reflexes*.—It has previously been stated that the differential sign between a reflex and a reaction is volition. Attention has also been called to the fact that a relatively small number of reflexes necessitate an impression in consciousness, otherwise, they cannot fully develop. These actions which skirt the realm of volition without being actually influenced by it, are desig-

¹ The Integrative Action of the Nerve System, Liverpool, 1906.

² Ewald, Pflüger's Archiv, xciv, 1903, 46

nated as perception or association reflexes. Thus, the flow of saliva or gastric juice may be elicited upon gaining a visual or olfactory concept of well-cooked food. Quite similarly, the yawning reflex may be evoked in us in consequence of a visual impression of some one else already engaged in this act; or we may receive stimuli tending to produce micturition at the sight or sound of running water. To this group also belongs the act of vomiting at the sight of foul food, as well as the so-called idiomotor movements. The latter consist in involuntary movements executed by us in imitation of the position of other people. Thus, we may follow the movements of a football player and find ourselves eventually in a state of muscular contraction without actually realizing how we got into it.

SECTION XV

THE FUNCTION OF THE SPINAL CORD

CHAPTER XLIX

THE SPINAL CORD AS A REFLEX CENTER—ITS POWER OF AUTOMATICITY

Localization of the Spinal Reflex Centers.—While it is true that the segmentalism so clearly betrayed by the lower forms, is also in evidence in the mammals, it must be admitted that it has lost much of its original conspicuousness on account of the development of the long conducting system and of those central complexes of neurons which give rise to psychic and other singular activities. In endeavoring to compare the conditions found in a typical segmental or reflex animal, such as the crayfish, with those existing in man, it may be advantageous to begin this discussion with a general survey of the structural and functional arrangement of the spinal paths in the intermediate groups of animals formed by the reptilia and amphibia. We have previously noted that a stimulus applied to the foot of a decerebrated frog, eventually induces muscular contractions which lead to a retraction of the leg from the seat of the stimulation (Türck's method). If the spinal cord is now thoroughly destroyed with the aid of a thin wire, it will be found that subsequent to this time the stimulus remains absolutely ineffective. This result proves that the destruction of the spinal cord has produced in this case a break in the circuit of this particular reflex. Secondly, as the receptor and effector, as well as the afferent and efferent paths, have not been interfered with in this instance, the aforesaid procedure must have led to a destruction of the center necessary for this reflex. Thirdly, inasmuch as all other reflexes occurring in the realm of the spinal cord, have also been abolished, the deduction may justly be made that this part of the nervous system contains the centers for a large number of reflex circuits and may, therefore, be regarded as an important seat of reflex action.

We have thus established one of the two most important functions of the spinal cord, the other being its power of conduction by means of which the actions of peripheral parts are correlated with those of the cerebrum and allied structures. It is probably not necessary to remind the student of the fact that the destruction of this part of the nervous system does not abolish all reflex action. Only those reflexes are

destroyed by this procedure which are normally mediated by the spinal cord. Thus, the large number of sympathetic responses continue even in the absence of the cord and the same holds true of those accomplished with the help of the cranial nerves, provided, of course, that the region of the medulla oblongata has been left intact.

In the frog, the spinal cord extends backward as far as the ninth vertebra, namely, to the prominence upon the dorsal aspect of its body. The tenth vertebra, or urostyle, continues onward from here and forms the dorsal wall of the long extended abdomen and pelvis. By cutting transversely across the cord, beginning at the level of the first vertebra, it is possible to show that the reflexes from the hind limbs are not abolished until the level of the cartilage between the sixth and seventh vertebræ has been reached. Any section distally to this point of the cord destroys the aforesaid reflexes immediately. The conclusion must, therefore, be made that the reflex center for the hind limbs is situated opposite to the seventh and eighth vertebræ (Fig. 294). It is generally designated as the "sciatic center," because the paths which connect it with the periphery are collected on each side in one bundle, known as the sciatic nerve. The latter arises by three roots and it can be shown by stimulation with weak electrical currents that these radicles possess a somewhat different function, because they innervate different groups of muscles and thus give rise to several specific movements of the leg. With the aid of very delicate electrodes, it can also be proved that a similar localization of function is present in the sciatic center itself.

This method of dividing the spinal cord at different levels has also proved that the centers for the muscles of the abdomen are situated anteriorly to the sciatic center and that the center for the fore limbs is located anteriorly to these. Several reflex and automatic centers are also found in the medulla oblongata, namely, those controlling the cardiac, respiratory and vasomotor activities. It is evident, therefore, that the spinal cord of the frog and allied animals contains a series of centers for simple reflex action and that a segmentalism exists in these animals which closely approaches that found in the vermes and crustaceæ.

Spinal Reflexes in the Mammals.—If the attempt is made to pursue similar methods of localization in the mammals, we are immediately confronted by several difficulties, one of which is the much greater susceptibility and sensitiveness of the nervous

FIG. 294.—DIAGRAM TO SHOW THE POSITION OF THE REFLEX CENTERS IN THE SPINAL CORD OF THE FROG.

BC and *BN*, Brachial center and nerve; *A*, center for the parts of the trunk; *SC* and *SN*, sciatic center and nerve. The numbers indicate the different vertebræ.

system of these animals to operative interferences. The profound general reactions following these operations, are commonly centered in the phenomenon of shock and the development of a hypersensitiveness which frequently overshadows the primary effect. But while it must be granted that the spinal cord of the higher animals does not exhibit quite so decided a segmentalism as that of the reptiles, amphibia and fish, it nevertheless evinces a decided tendency at localization of function. Sherrington,¹ for example, has shown that the decapitated cat reacts to stimulations of the skin either by scratching movements or by flexion and extension of the legs. In fact, it is easily noted that a decerebrated animal, or one in which merely a part of the cerebral cortex has been removed, exhibits an even greater number of reflexes than a normal animal. Quite similarly, the division of the spinal cord at a point posterior to the nuclei of the phrenic nerves does not materially affect the reflexes from the posterior extremities. The patellar and other deep reflexes are not destroyed thereby.

Besides these centers which are solely concerned with reactions of skeletal muscle, it has been proved that the spinal cord also contains centers for several reflex acts of different character, as follows:

(a) Dilatation of the pupil. This center lies opposite the 1.-3. thoracic vertebrae. The motor fibers leave by the anterior roots and enter the upper thoracic nerves and the cervical sympathetic, terminating finally in the ganglion cervicale superior.

(b) The center for defecation, or centrum anospinale, is situated opposite the fifth lumbar vertebra (dog). The afferent path is formed by the plexus hemorrhoidalis and the efferent path by the nervus hypogastricus.

(c) The center for micturition, or centrum vesicospinale, is situated in the lumbar or sacral segment of the spinal cord. The nervi hypogastrici and erigentes constitute the efferent path.

(d) The centers for the erection of the male and female generative organs are situated in the lumbar portion of the cord. The arteria profunda penis is innervated by the vasomotor fibers of the 1.-3. sacral nerves, while the 3. and 4. sacral nerves activate the musc. ischiocavernosus and transversus perinei profundus.

(e) The center for ejaculation is also placed in the lumbar segment of the cord.

(f) The center for the contraction of the uterus is located in the lumbar segment of the cord.

(g) The centers in the bulbar enlargement of the cord, i.e., in the medulla oblongata, regulate the activity of the heart, the respiratory movements, the caliber of the blood-vessels, deglutition, reversed deglutition or vomiting, heat dissipation, and other functions.

In view of this rather well marked segmentalism, it cannot be denied that the spinal cord of the higher animals possesses a functional arrangement very similar to that present in the lower forms. It is an important seat of reflex action. But, inasmuch as the cerebrum gradually gains a more complete control over these simple functions, the spinal centers lose their independency of action. This is especially true of man, because, somewhat contrary to the results obtained in the dog, cat and rabbit, the complete division of the spinal cord is followed

¹ Jour. of Physiol., xxxviii, 1909, 375.

in this case by an abolition of the reflexes and a general loss of irritability of the nervous structures situated posterior to the cut.¹ A partial division of the cord, however, is often recovered from without permanent loss of function.

In this connection, brief reference should also be made to the experiments of Goltz,² purposing to arrive at a definite conclusion regarding the function of the spinal cord by the method of total or partial extirpation. In the mammals, the former procedure is not feasible, for the reason that the phrenic nerves take their origin from its cervical portion. Any interference with the phrenic nuclei would cause a stoppage of the respiratory movements. Goltz, therefore, removed the cord merely as far as its upper thoracic segment, special care being taken to protect these animals against an undue loss of heat and other injurious influences. Those surviving the operation, showed a complete motor paralysis which eventually gave way to an atrophic condition of these parts. They also exhibited a complete sensory anesthesia, and although their vasomotor and other autonomic functions remained depressed for some time after the operation, the vascular tonus reappeared in a large measure. In addition it was noted that the ordinary pelvic reflexes again assumed their original qualities. These results indicate very clearly that the sympathetic system is relatively independent of the spinal cord and other parts of the central nervous system, because the digestive, secretory, circulatory and excretory organs eventually regained their functions after the destruction of the cord. Various other symptoms, however, such as a gradual lowering of the body temperature and a very decided loss of adaptation of the parts formerly innervated by the destroyed portion of the cord, suggested that the animal was no longer able to influence its autonomic organs and to correlate their functions with those of other structures.

The Automatic Activity of the Spinal Cord.—Having established the fact that the spinal cord is an important seat of reflex action, it should be noted that several of the centers situated within the domain of the cord and bulb, are automatically active. Admittedly, an automatic action finds its origin neither in volition nor in sensory impressions of the ordinary intermittent type. Its cause must rather be sought in an "inner" stimulus which arises in consequence of constant and specific stimulations and renders the center self-inducing. The question of whether the centers of the spinal cord possess automatic qualities, must be answered in the positive and especially if the medulla oblongata is taken to be a part of this structure. Thus, it is a well known fact that the cardiac, respiratory and vasomotor centers are composed of cellular elements which generate impulses rhythmically in consequence of inherent stimuli. While it is entirely probable that the centers situated in the more posterior segments of the cord possess a much slighter automatic power than those just mentioned, it must nevertheless be admitted that they generate impulses at regular

¹ Collier, Brain, 1904, 38.

² Pflüger's Archiv, lxxviii, 1896, 362.

intervals. Moreover, as these impulses are intended merely to produce a tonic setting of the peripheral musculature, the aforesaid spinal centers may be said to be tonically automatic, in contradistinction to the bulbar centers, which may be considered as being rhythmically automatic.

It must be admitted, therefore, that the ganglion cells composing these centers are in a state of constant tonic activity. This implies that they produce "subthreshold" impulses at regular intervals which tend to retain the effector in a condition of functional alertness ready at any time to yield maximal effects. Conversely, it may be concluded that the loss of these impulses must diminish the tonus of the effector and induce atrophic changes. You will have noticed that the legs of a decerebrated frog, suspended from a hook, assume a definite position of flexion, because the muscles are still in connection with the motor cells of the cord. If one of the sciatic nerves is now cut, the muscles on the side of the lesion immediately relax and allow the leg as a whole to assume a more dependent position. In view of the fact that these changes cannot be observed in a reflex frog after the skin has been removed or after the posterior roots of the spinal cord have been divided, it has been assumed that the tonic automaticity of the spinal ganglion cells is due to a constant influx of subminimal sensory impulses from the cutaneous receptors. In other words, it is assumed that the "inner stimulus" imparted to the motor cells of the cord, finds its origin in sensory impulses of such slight intensity that they cannot incite muscular contraction. Hence, the tonus of a muscle is really a subminimal reflex phenomenon. The inherent or inner stimulus upon which the automatic power of a nerve cell depends, may thus be referred to subminimal sensory stimuli.

Superficial, Deep, and Organic Reflexes.—In man, the spinal cord aids in the production of a number of reflexes which possess a very distinctive character and may on this account be employed for purposes of diagnosis. Among the superficial or skin reflexes may be mentioned the:

(a) *Cremasteric Reflex.*—This reaction is elicited best by gently rubbing across the inner aspect of the thigh. It consists in a raising of the scrotal sac and testicle in consequence of the contraction of the *musc. cremaster*.

(b) *Scrotal Reflex.*—It presents itself as a contraction of the *tunica dartos* in consequence of an excitation applied to the skin of the scrotum.

(c) *Sternal and Abdominal Reflexes.*—These reactions may be evoked by rapidly drawing the blunt end of a rod-like instrument across the external surface of the chest or abdominal wall. It consists in a contraction of the neighboring muscles.

(d) *Scapular Reflex.*—It results in consequence of excitations of the skin in the vicinity of the spinal column. The *musc. rhomboidei* contract.

(e) *Pharyngeal Reflex.*—The touching of the posterior wall of the pharynx incites a contraction of the muscles lining this passage.

(f) *Mamillary Reflex.*—The stimulation of the integument in the vicinity of the nipple is followed by an erection of the papilla.

(g) *Gluteal Reflex.*—The *musc. gluteus maximus* contracts in consequence of stimuli applied to the skin covering the buttocks.

(h) *Plantar Reflex*.—It consists in a flexion of the toes in consequence of tactile stimulation of the sole of the foot. In certain affections of the pyramidal tracts of the cord, this stimulation elicits an extension of the great toe, instead of a flexion. This constitutes the so-called Babinski phenomenon.

(i) *Bulbocavernosus Reflex*.—This muscle may be made to react to stimuli applied to the glans penis.

(j) *Reflexes from the mucosa* may be elicited by stimulation of different mucous surfaces.

(k) *Winking Reflex*.—The eyelids are closed if a stimulus is applied either to the cornea, conjunctival membrane or skin covering the eyelids.

(l) *Reflexes from the Facial Muscles*.—These responses are obtained by stimulating the skin in vicinity of these muscles.

Among the so-called deep reflexes, *i.e.*, reflexes which are elicited by stimulations of the tendons, ligaments and periosteum, may be mentioned the:

(a) *Patellar Reflex or Knee-jerk*.¹—A slight stroke upon the ligamentum patellæ produces a contraction of the musc. quadriceps femoris, involving especially the musc. vastus medialis and vastus intermedius. The best results are obtained if the muscle is first put under a slight tension which end can readily be attained by crossing the knees or by sitting upon a chair or table and permitting the leg to hang free across its edge.

(b) *Achillis Jerk*.—If the foot is placed in the position of dorsiflexion, a tap upon the tendo calcaneus (Achillis) evokes a contraction of the musc. gastrocnemius and plantar flexion of the foot. The so-called ankle clonus is obtained if the foot is quickly flexed so that the tendo Achillis and musc. gastrocnemius are suddenly stretched. In certain nervous disorders this reaction acquires a periodic character.

(c) *Wrist Jerk*.—This reflex is obtained by tapping the tendons of the muscles of the forearm. Similar effects are yielded by the musc. gracilis, semitendinosus, triceps and biceps.

(d) *Jaw Jerk*.—The jaws are closed if the lower jaw is tapped when in the half-open position.

(e) *Periosteal Reflexes*.—The musc. supinator longus and biceps contract if the head of the radius is tapped upon.

(f) *Tensor Tympani Reflex*.—The musc. tensor tympani contracts as a result of sound impacts of high pitch. The ear drum is in this way rendered more tense.

The organic or visceral reflexes have been enumerated in part above. They include those pertaining to micturition, defecation and the sexual activities. They are executed chiefly with the help of smooth muscle and glandular tissue, while the superficial and deep reflexes are largely concerned with striated muscle.

The Nature of the Patellar Reflex.—While the question whether or no the knee-jerk is a true reflex, has been decided in favor of the first view, this decision has not been reached without considerable discussion. To begin with, it was thought that it could not be a true reflex, because the time interposed between the stroke upon the patella and the contraction of the musc. quadriceps, is altogether too short to permit of the passage of the impulse through the spinal cord. This view was based upon the early calculations of the speed of the nerve impulse which, in accordance with Helmholtz, amounts to 33 m. in a second in warm-blooded animals. It was believed, therefore, that the sensory impulse does not enter the spinal center at all, but is transferred to the muscle by way of a peripheral collateral. If this conception were correct, the patellar reflex should really be

¹ Discovered by Erb, *Archiv für Psychiatrie*, v. 1875; and Westphal, *ibid.*, 1875.

regarded as a pseudo or axone reflex, *i.e.*, as one which is had without the intervention of the cell-body or center. In other words, the impulse set up in the receptor, passes no farther than the next collateral, where it finds a direct course to the effector. This explanation, as has just been stated, was intended to bring the extremely brief time of the patellar reflex into relation with the speed of the nerve impulse, as determined by the older methods. Applegarth, for example, has stated that the patellar reflex time is 0.014–0.02 sec. (dog), while Waller and Gotch found it to be 0.008–0.005 sec. (rabbit). Later on, however, it has been shown by means of the string galvanometer, that the speed of the nerve impulse in warm-blooded animals may amount to more than 100 m. in a second. In addition, Snyder¹ and Hoffmann² have ascertained that the patellar reflex time lies somewhere between 0.0113 and 0.024 sec. These figures, therefore, prove very conclusively that the patellar reflex must involve the spinal center; at least, the time allowed for it is sufficient to complete the entire circuit from the ligament to the cord and back again to the muscle.

The objection has also been raised that the contraction of the musc. quadriceps is a simple twitch and not a tetanus, as is usually the case when muscles are activated reflexly. Much has also been made of the fact that the aforesaid muscle reacts best when subjected to a slight tension. It has been found, however, that not all muscular responses are tetanic in their character. Sherrington,³ for example, has called attention to the fact that the so-called "extensor thrust" which may be obtained in animals by suddenly pressing upon the plantar surface of the hind foot, consists of simple contractions of the extensor muscles of the hind leg. Lastly, it has been proved that any injury to the lumbar segment of the spinal cord destroys the patellar reflex and that its abolition may also be effected by dividing either the posterior or the anterior roots of the cord. Obviously, therefore, the production of the patellar reflex necessitates not only an intact spinal center but also intact centripetal and centrifugal paths. Its reflex nature, therefore, seems to be thoroughly established. A similar controversy has led to the establishment of the fact that the Achilles jerk is a true reflex.

Reinforcement of Reflexes.⁴—In testing the different reflexes, it soon becomes apparent that the subject must remain in a state of perfect inattention, otherwise the response will be less intense, or may, in fact, be entirely abolished. In other words, if the attention of the subject is directed to the procedure of eliciting the reflex, the usual result is its inhibition by the cerebral centers. In this way, a diagnosis of abolition of reflexes may be made which in reality is nothing more than a normal phenomenon. This difficulty may be easily overcome

¹ Am. Jour. of Physiol., xxvi, 1910, 474.

² Archiv für Physiol., 1910, 223.

³ Jour. of Physiol., xxxviii, 1909, 375.

⁴ First observed by Jendrassik in 1883.

if the subject is asked to engage in some mental process while the stimulus is brought to bear upon his integument or tendons. The reflexes may also be augmented by asking the subject to make a volitional muscular effort at the time the blow is struck. This requires a certain mental concept and it is conceivable that the activation of the cerebrum temporarily abolishes its inhibitory power, and thus diminishes the resistance along the different reflex circuits. Under ordinary conditions, the patellar reflex may be heightened very materially by simultaneously contracting the muscles of the hands or by endeavoring to pull the interlocked fingers apart. But, while we are able in this way to intensify a feeble jerk, no effect can be produced after the reflex has been abolished by disease.

This phenomenon which is usually described as reinforcement of reflexes,¹ also permits of a second explanation. It is commonly recognized that the functional activity of one part of the nervous system also influences the irritability of others. Thus, it may rightly be assumed that the activation of the cerebrum, accompanying such actions as the interlocking of the hands or fingers, renders this organ more irritable. The motor impulses thus generated in its cortical area, escape through the descending columns of the cord, where they skip to neighboring columns and nuclei and give rise to a general activity of these nervous elements. In other words, the constituents of the spinal reflex circuits are sensitized by an overflow of the cerebral impulses. It is quite impossible at this time to decide definitely which of these two theories is the more correct. Obviously, the first more closely agrees with the common phenomenon of inhibition of reflexes by the cerebral centers, while the second introduces a rather new factor in the form of an activation of certain parts of the nervous system which lie at some distance from the seat of the primary process.

It should also be noted that the reinforcement does not develop if the interval of time between the simultaneous effort and the excitation is too long. Thus, it has been shown by Bowditch and Warren² that the knee-jerk suffers its greatest augmentation if the blow upon the tendon precedes the reinforcing action by less than 0.6 to 0.9 sec. A greater interval will tend to minimize the reinforcement until it eventually gives way to an inhibition. This diminution of the reflex in consequence of a premature simultaneous effort is designated as negative reinforcement.

Abolition and Exaggeration of the Reflexes.—With few exceptions, reflexes may be regarded as a safe index of the relative state of irritability of the nervous system, provided, of course, that the method of stimulation is free from error. But even a perfectly normal body undergoes diurnal and seasonal changes which reflect their influences upon reflexes. Thus, we find that they are weakened during sleep and other states of mental rest; in fact, some of them are abolished entirely

¹ Mitchell and Lewis, *Am. Jour. of the Med. Sciences*, xlii, 1886, 363.

² *Jour. of Physiol.*, ii, 1890, 25.

during these periods. Conditions of mental excitement and general neurasthenia, on the other hand, increase them very markedly.

While one or the other of the reflexes enumerated previously may be absent in a perfectly healthy person, their general abolition suggests in most cases a pathological lesion of some kind. This defect may be restricted to a particular reflex circuit or may involve more extensive areas of the nervous system. In the first instance, the break must have occurred at some point of the reflex arc which now fails to respond even on reinforcement, while, in the second instance, a more general or central depression of the nervous system must have resulted. In illustration of the first condition might be mentioned the loss of a particular superficial or deep reflex of the spinal cord in consequence of acute anterior poliomyelitis which infection destroys the motor cells in the anterior horn of the gray matter. Reference might also be made to tabes dorsalis in which affection the posterior root terminals in the cord are destroyed, thereby causing a break in the central distribution of the analyzer. Among the general depressions of the nervous system producing diminution or abolition of the spinal and other reflexes, might be mentioned increases in intracranial pressure, such as result in hydrocephalus or in consequence of cerebral tumors. They are also abolished for a time in comas and epileptic seizures and certain febrile reactions, such as pneumonia.

Reflexes are said to be exaggerated when the slightest possible stimulus elicits an unusually brisk motor response. This is a common phenomenon in simple neurasthenia and hysteria and other conditions in which the irritability of the nervous system has been increased in consequence of the absorption of various poisons, such as the products of intestinal fermentation, strychnin, caffeine, thebein, and others. In many cases the reflexes are then augmented into clonic contractions which are maintained until the tension upon the tendon is again released. Clearly, therefore, the presence of a true clonus¹ implies that the reflex arcs are in a state of hyperirritability. In this connection, brief reference should also be made to the fact that the exaggeration of the spinal reflexes constitutes a cardinal sign in chronic affections involving the motor neurons of the cerebrum. In general, it may be said that a "high" (cerebral) lesion leads to an exaggeration and a "low" (spinal) lesion to an abolition of the reflexes. It cannot surprise us, therefore, that an affection of the motor areas and pyramidal tracts is generally associated with clonic contractions. As typical examples of this condition might be mentioned hemiplegia from organic brain disease, or paraplegia due to myelitis. Incomplete transections of the cord, as often result in fractures of the spine, produce exaggerated reflexes, while complete transections are usually followed by a loss of the deep reflexes.

These differences may be explained in the same way as the phe-

¹Spurious clonic reflexes are obtained at times in hysterical conditions. They are usually irregular and poorly sustained.

nomenon of reinforcement of reflexes. Thus, we may assume that a "high" lesion tends to remove the central inhibition and to cause a "Bahnung" of the reflex circuits, or, that a "high" lesion gives rise to an increase in the irritability of central parts which in turn induces a similar condition in other divisions of the nervous system. In brief, we may explain this phenomenon either upon the basis of removal of cerebral inhibition or upon the basis of an overflow of irritability from this organ. At all events, the facilitation of the spinal reflexes in consequence of central lesions, finally throws the paralyzed muscles into a state of continued contraction or contracture, their spastic rigidity eventually leading to contortions of the extremities. But a paralysis of the muscles is also present in "low" lesions, because these organs then lose the volitional and tonic impulses from the spinal centers. In the latter case, however, the muscles remain in a perfectly flaccid condition and finally undergo atrophic changes from disuse. These differences in the intensity of the reflexes and in the behavior of the muscles are usually so typical that they may be employed in ascertaining the exact location of the lesion.

CHAPTER L

THE SPINAL CORD AS A CONDUCTING PATH—ITS TROPHIC FUNCTION

The General Structure of the Spinal Cord.—We have previously noted that the spinal cord in the invertebrates consists of a series of ganglia which severally regulate the activities of those segments of the body to which they have been apportioned. In further development of this simple reflex system, the different ganglia have been connected with one another and with the head-ganglion by means of a system of afferent and efferent fibers which pursue a course parallel to the longitudinal axis of the body. This primitive segmental arrangement is also in evidence in the vertebrates, with this modification, however, that the reflex functions no longer exhibit a strictly local character but are now more closely correlated and subordinated to the activities of the higher centers. This change necessitates first of all the development of a system of conducting paths which connect the different spinal centers with one another, and fuse them into a harmonious whole. In the second place, it necessitates the formation of certain conducting paths which connect these simple centers with those situated in the brain. In this way, two types of conducting channels have been formed, namely, the short and the long. The former represents the more primitive reflex system over which eventually the

long reaction system has been constructed. For this reason, it may be stated that reflex action is a more primitive function than the type of conduction seen in the higher animals. But, while the spinal cord of the latter has lost much of its simple reflex character, it cannot be denied that it still displays it in a clearly recognizable manner. Thus, we have seen that this structure contains a series of centers for superficial, deep and organic reflexes, and that the location of these centers

roughly corresponds to the seats of these actions, *i.e.*, they are arranged in accordance with a definite segmental pattern. In addition, the succeeding discussion will show that this segmentalism and dissociation of function has also entered into the construction of the conducting paths.

FIG. 295.—THE MEMBRANES OF THE SPINAL CORD.

1. Dura mater. 2. Arachnoid.
3. Posterior root of spinal nerve.
4. Anterior root of spinal nerve. 5. Ligamentum dentatum. 6. Linea splendens. (*After Ellis.*)

FIG. 296.—TRANSVERSE SECTION THROUGH THE REGION OF THE FOURTH CERVICAL VERTEBRÆ.

V, Body of vertebra; B, vertebral blood-vessels; N, spinal nerve; RC, ramus communicans; S, spinal ganglion; A, subarachnoidal space investing spinal cord.

The spinal cord of man appears as a cylindrical structure which extends into the vertebral canal for a distance of 40–45 cm., *i.e.*, to the level of the second or third lumbar vertebra. Beyond this point it continues as a narrow thread, called the *filum terminale*. It measures 12 mm. in diameter and weighs 42 grams. From it arise thirty-one pairs of nerves, in serial order so that each pair corresponds to a vertebra and innervates symmetrical areas upon the two sides of the body. The spinal nerves are mixed nerves, *i.e.*, they consist of afferent and efferent fibers connecting central parts with their respective receptors and effectors. It is to be noted, however, that they do not arise as such directly from the cord, but originate as two compact bundles, one of which lies in close relation with the anterior and the other with the posterior aspect of this structure. The former constitute the anterior (ventral) root and are efferent in their nature, while the latter form the posterior (dorsal) root and conduct only in an afferent direction. These two groups of fibers are joined in the intervertebral foramina, their point of union being roughly marked by a ganglion composed of the cell-bodies belonging to the sensory fibers of the posterior root. The nerves which are distributed to

the arms and legs arise from the lower cervical and lower lumbar regions respectively. It is for this reason that these particular segments of the cord are somewhat broader than the others, and present an elliptical outline, whereas the dorsal region is almost circular.

In cross-section the spinal cord is found to be composed of a central mass of gray matter which is surrounded on all sides by a shell of white matter. The former appears on each side in the form of a crescent, the convex surface of which is turned inward and is joined with the one in the opposite half of the cord by a transverse band or commissure. The entire mass of gray matter roughly exhibits the shape of the letter H, and is divided on each side into an anterior or ventral and a posterior or dorsal horn, the intervening substance being known as the intermediate gray matter. The anterior horn is short and bulky, while the posterior horn is narrow and slender, extending to the surface of the cord where it

FIG. 297.—CROSS-SECTION THROUGH THE HUMAN SPINAL CORD AT THE LEVEL OF THE FIFTH CERVICAL NERVE, STAINED BY THE METHOD OF WEIGERT-PAL, WHICH COLORS THE WHITE MATTER DARK AND LEAVES THE GRAY MATTER UNCOLORED. (From Cunningham's *Anatomy*.)

is invested by the substantia gelatinosa. The latter is known as the *caput cornu posterioris*. In the lower cervical and thoracic regions, the intermediate gray matter becomes unusually prominent and forms here the so-called lateral horn. The center of the commissure uniting the right and left halves of the gray matter, is occupied by a canal (0.5–1.0 mm. in diameter) which extends throughout the entire length of the cord, and eventually communicates with the lymphatic spaces of the brain. This is the remains of the primitive neural canal of the embryo. It is surrounded by substantia gelatinosa and its walls are lined with cylindrical epithelium. It is filled with liquor spinalis, a lymphatic fluid of the same character as the liquor contained in the cerebral spaces.

The white matter of the spinal cord is made up of different bundles of sensory and motor fibers which are arranged in such a way that they fill in the different spaces externally to the gray matter. They are medullated, but possess no neurolemma and run within tubes formed by the supporting neuroglia tissue. Inasmuch as the entire mass of the spinal cord is divided into two halves by the anterior and posterior median fissures, the white matter of each side presents itself in

three columns or funiculi, namely: (a) one situated between the anterior furrow and the anterior horn of the gray matter, (b) one neighboring upon the lateral surface of the gray matter and (c) one located between the posterior fissure and the posterior horn of the gray matter. We shall see later on that the anterior, lateral and posterior funiculi are in turn made up of several tracts or fasciculi which are anatomically and functionally distinct from one another. It is also to be noticed that the median fissures do not extend directly to the commissure of the gray matter, but permit bridges of white matter to intervene. These are the so-called anterior and posterior commissures. The fissures themselves contain a process of the pia mater which invests the external surface of the cord, and, together with the arachnoid and dura mater, forms a protective envelope for this structure.

The Functional Basis of the Gray Matter.—The gray matter consists of the supporting neuroglia in which are imbedded numerous cell-bodies and the beginning portions of their processes. The former appears as a felt-like network of fibers with scattered nuclei. Around the central canal and in the vicinity of the entrance of the posterior

FIG. 298.—A NEUROGLIA-CELL, ISOLATED IN 33 PER CENT. ALCOHOL. (Quain.)

root, these reticular spider-shaped cells are especially small and numerous, forming here the so-called substantia gelatinosa of Rolando. The nerve cells of the spinal cord are very numerous and exhibit a variety of shapes and sizes. It should also be noted that they occupy definite areas of the gray matter and extend as distinct colonies for some distance up and down in the cord. In the anterior horn, where they are especially promi-

nent, they are arranged in three groups. The median group is situated near the middle line and its axons may be traced across to the other side through the anterior commissure of the white matter. The anterior group consists of large multipolar cells, the axons of which pass outward in the anterior roots of the cord and are distributed eventually to the different effectors of the spinal system. Some of these cells, as we shall see later, send their axons into neighboring sympathetic ganglia and thus form the efferent bridges between the cerebrospinal and sympathetic systems. The aforesaid cells are especially numerous in the cervical and lumbar segments of the cord which, as we have seen above, innervate the anterior and posterior extremities. The posterior group of cells is present in those regions of the cord in which the lateral horn is well developed. A very prominent column of cells also extends through the dorsal and inner area of the cord near the base of the posterior root. These cells begin at the level of the seventh or eighth cervical nerve and reach downward as far as the second or third lumbar nerve. They are most conspicuous in the thoracic region, their large bodies being elongated in the longi-

tudinal axis of the cord. Their axons tend obliquely outward into the so-called direct cerebellar tract of the lateral white matter. Some of these processes also pass into the fasciculi next to the posterior median fissure. Posterior to this group of cells, constituting the so-called Clarke's vesicular column, we find a few cells distributed in an irregular manner through the posterior horn. The cells of the sensory fibers forming the posterior roots, are, of course, situated outside the cord, in the spinal ganglia.

When considered from the standpoint of gross and minute anatomy, the white matter of the spinal cord presents itself as three funiculi which in turn are divided into several fasciculi. The physiologist, however, is more directly concerned with the function of these collections of nerve fibers and hence, his unit is the tract, *i.e.*, bundles of fibers possessing an identical action. But as several of these tracts have clearly defined anatomical boundaries, these terms are frequently used interchangeably. As far as the cells of the gray matter are concerned, it is important to determine the tracts to which

FIG. 299.—SPINAL GANGLION OF AN EMBRYO DUCK; COMPOSED OF DIAXONIC NERVE-CELLS. (*van Gehuchten.*)

these cells are functionally related. Upon this basis we may divide them into two main groups, namely, *local* and *general*. As the former are intended to establish a close relationship between the cells situated in different parts of the gray matter and at different levels of the cord, they are associative (tantomeric) or commissural (heteromeric) in their nature. In this class should be placed the cells of Clarke's column, because they are tributary elements to the direct cerebellar and posterior tracts. The same is true of the cells of the median group, because they send their axons across the middle line to the opposite gray matter and thus become commissural in their nature. Another type of associative cell is the cell of Golgi which is found chiefly in the posterior horn. Its axon does not pass far away from the cell-body, but ramifies extensively to establish connections with neighboring cells at any level of the cord.

The group of the general cells is made up of those cells which are concerned with bringing the cord into relation with the higher centers as well as with the peripheral end-organs. Chief among these are the large ganglion cells in the anterior horn, measuring 57

to 135μ . They are efferent in their nature and innervate the skeletal musculature. Second in importance are the somewhat smaller cells of the lateral horn, the axons of which leave the cord by way of the anterior roots but finally separate to enter the sympathetic ganglia. In this way, the white ramus communicans is formed, constituting one of the efferent bridges between the cerebrospinal and sympathetic systems. As has been stated above, the afferent cells of the cord are contained in the spinal ganglia which are situated upon the different posterior roots. Other afferent cells of the projection system form the nucleus gracilis and cuneatus, the end-stations of the posterior fasciculi.

FIG. 300.—SPINAL GANGLION-CELLS SHOWING TRANSITION FROM BIPOLAR TO UNIPOLAR CONDITION. (Holmgren.)

The Functional Basis of the White Matter—The characteristic appearance of the gray matter and white matter is dependent upon certain structural differences. The former is composed principally of cell-bodies and the dendrites and axons in their immediate vicinity, while the latter consists chiefly of axons enveloped in their medullary sheaths, in other words, of nerve fibers. It is evident that the white matter decreases constantly in the direction toward the tip of the cord, because the number of fibers still retained at its lumbar level is much smaller than that near the medulla. Fibers leave this structure all the time to reach peripheral parts, and fibers enter it continuously to attain the higher centers. This does not imply, however, that there is an absolute proportion between these fibers and the total area of the white matter at different levels of the cord, because a large number of them do not pass all the way through, but form merely local reflex connections. In addition, it should be noted that the relative amounts of gray and white matter vary at different levels of the cord, thereby enabling us to determine with accuracy from what particular area any given section has been taken. Sections from its lumbar region are characterized by a copious amount of gray matter, while those from its cervical portion are relatively poor in this substance. Besides, as especially large numbers of fibers arise in its cervical and lumbar segments at the points of origin of the plexuses of the arms and legs, the total cross-area of the cord must be markedly increased at these levels.

The posterior roots serve as points of entrance for about half a million fibers and we may assume that an equal number leaves by way of the anterior roots. The afferent impulses which are in this

way poured into the central nervous system are of different kinds and may either remain within the domain of the cord or may be conveyed onward to higher centers. The same holds true of the efferent impulses. While some of them arise in the brain and neighboring parts, some also originate in the motor cells of the cord itself. Obviously, therefore, the conduction system of the cord is arranged in the form of a long or projection system and a short or reflex system. The latter is the more primitive, and hence, we find that it occupies a position next to the gray matter, while the projection paths correlating peripheral parts with the brain, form the external shell of the spinal white matter.

The axons of the nerve cells uniting these widely separated portions of the nervous system, are of different lengths. It is said that the motor neurons in the anterior horn of the spinal gray matter reach all the way to the periphery and attain a length of 1.0 m. The same holds true of the motor cells of the cerebral cortex, the axons of which terminate low down in the cord. In many cases, however, two or three neurons are required to cover a distance of only a few centimeters. In adult life, the axons of the spinal white matter are surrounded by medullary sheaths but not by neurolemma. They differ, therefore, in this regard from ordinary nerve fibers. They are of different size and give off small collaterals which connect with the gray matter at different levels of the cord. Externally, they are invested by a tube formed by neuroglia tissue.

The Methods Used for the Localization of Spinal Conduction.—We have previously seen that the white matter of the cord is arranged as anatomically distinct bundles. The question may now be asked whether these morphological units also represent physiological entities. In other words, can it be proven that the different fasciculi possess a different origin and destination so that their direction of conduction assumes a specific character? While the investigations pertaining to this topic cannot be

FIG. 301.—SECTIONS THROUGH DIFFERENT REGIONS OF THE SPINAL CORD.

A, At the level of the sixth cervical nerve; B, at the mid-dorsal region; C, at the center of the lumbar enlargement; D, at the upper part of the conus medullaris. 1. Posterior roots. 2. Anterior roots. 3. Posterior fissure. 4. Anterior fissure. 5. Central canal. (After Schwalbe.)

regarded as at all complete, the material already at hand suffices to show that the spinal cord contains definite tracts which in the main correspond with the anatomical grouping previously discussed. The methods employed to trace the course of these different neuron systems are as follows:¹

(a) *Morphological*.—Different procedures of *staining* have been made use of in order to differentiate the cell-bodies and their processes more clearly from the surrounding tissue. The impregnation procedures of Weigert and Golgi consist in hardening the preparation in chromate or bichromate and subjecting it subsequently to a solution of silver nitrate or mercuric chlorid. The silver or mercuric chromate precipitates are not diffuse, but are restricted to certain parts of the neuron and may be bleached sufficiently to allow the tracing of the processes in

FIG. 302.—SCHEMA OF THE TRACTS IN THE SPINAL CORD. (Kolliker.)

g, Fasciculus gracilis; *b*, fasciculus cuneatus; *pc*, fasciculus cerebrospinalis lateralis; *pd*, fasciculus cerebrospinalis anterior; *f*, fasciculus cerebellospinalis; *gr*, fasciculus anterolateralis superficialis.

rather thick sections. Ehrlich has advocated the intravital staining with methylene-blue.

The method of differential staining is frequently employed as a means of recognizing medullated and non-medullated nerve fibers. It has been pointed out by Flechsig that the newly-formed axons are non-medullated, but acquire a sheath when developed sufficiently to become functional. Now, as the different parts of the nervous system attain their full development in a definite sequence, it cannot surprise us to find that the *myelination* of the various fiber groups takes place successively and at certain intervals from one another. Moreover, as the projection system is the most recent acquisition of the nervous system, we are justified in assuming that the pyramidal tracts, connecting the cerebrum with the cord, re-

¹ Galenus compared the spinal cord to a stream which distributes nervous energy to all parts of the body. Oribasius describes the effects following sections of the cord. These are also discussed in the writings of Hippocrates.

ceive their medullary coverings last of all. In this assumption we are correct, because the myelination of these fibers is not completed until the first month after birth. Next in order follow those fibers which connect the cerebellum with the spinal cord. These also belong to the long system. Following the same course of reasoning, it may be assumed that the fibers composing the more primitive system, which regulates the reflex life of the animal, acquire their medullary sheaths long before the others. In this assumption we are also correct, because the fibers connecting the centers in the spinal cord with the sensory and motor organs at the periphery, are myelinated first. From here the myelination progresses to those intraspinal fibers which connect the different segments of the cord. In the human embryo, this process is practically completed at the time of birth.

The third morphological method consists in *tracing the course of degenerating nerve fibers*.¹ It has been pointed out above, that a nerve fiber, when separated from its cell-body, is eventually converted into a band-fiber. This process necessitates the conversion of the phosphorized fat of the myelin into fat which is absorbed and displaced by fibrous tissue. In studying the distribution of the spinal fibers, it is possible to divide the cord in places and to trace the degenerating fibers by the method of staining. The sections are hardened in a bichromate solution and are then placed in a mixture of osmic acid and bichromate. Normal myelin remains unstained, while its fatty derivative assumes a black color. Obviously, the degeneration of a tract above the section implies that the trophic centers (cell-bodies) of these fibers are situated below the lesion and that the degeneration is ascending in its character. Quite similarly, a degeneration below the cut signifies that the cell-bodies are located above the lesion and that the degeneration is descending in its nature. This method has been employed by Waller in his determination of the function of the roots of the cord.

It should also be remembered that the localization of the cell-bodies of a given tract of fibers does not always necessitate a repeated transection of the cord at different levels, but may also be effected by means of staining the suspected cells. It has been pointed out above that the degeneration following upon the separation of a nerve fiber from its cell-body, does not remain confined to the peripheral stump of the cut fiber, but also involves its central end and corresponding cell-body. This central degeneration which is known as retrogressive degeneration, finds its cause in a trophic disturbance of the cell-body in consequence of the inactivity forced upon it by its separation from its end-organs and neighboring neurons. In their final atrophic state, these cells may readily be recognized after staining with methylene blue or toluidin blue. They exhibit a swollen and eccentric nucleus as well as indistinct and diffusely stained chromophil granules.

(b) *Physiological*.—The early view of VanDeen and Schiff, that the white matter of the spinal cord is non-receptive to electrical stimuli, has been thoroughly disproved by the work of Fick, Biedermann, and others. It must be admitted, however, that the results of the direct *stimulation* of the different tracts of the cord leave much to be desired, because the paths are not sufficiently separated from one another to be able to obtain sharply differentiated effects. In spite of this difficulty this method has proved distinctly helpful as an adjunct to other procedures. By applying a galvanometer or capillary electrometer to the different spinal paths, Eckhard, Gotch and Horsley² have succeeded in *tracing the action current* which is produced whenever the motor areas of the cerebrum are stimulated. This method has been amplified by the procedure of fractional division of the spinal cord. Obviously, the division of certain spinal tracts enables us to determine whether these electrical variations continue even after the establishment of this block between the motor area and the level of the galvanometer. This procedure is also applicable to the tracing of the circuits of the common spinal reflexes.

¹ Employed by Türck in 1851 upon sections of the diseased spinal cord of man.

² Proc. Royal Society, London, 1888.

FIG. 303.—SCHEMA ILLUSTRATING THE EXPERIMENT FOR DETERMINING THE NUMBER OF SEPARATE NERVE IMPULSES PASSING DOWN THE SPINAL CORD UPON STIMULATION OF THE CORTEX. (Horsley.)

E, E, electrodes, intended to be on the "leg area." Where the cord is interrupted, one non-polarizable electrode is placed over the cut end of the pyramidal fibers going to the lumbar enlargement; the other, on the side of the cord. These lead to the capillary electrometer, in which the column of mercury moves each time an impulse passes.

(c) *Clinical Observations.*—A study of the clinical pictures of diseases of the spinal cord must prove of especial value if the symptoms are subsequently compared with the record of the autopsy. Naturally, the difficulties connected with an accurate localization of motor and sensory defects are minimized in man, owing to his ability to observe and to describe his own symptoms.

Classification of the Fasciculi of the Spinal Cord.—The white matter of the spinal cord is divided into three fasciculi, an anterior, a lateral and a posterior.¹ The first two are often called the antero-lateral fasciculi, because the rather scattered distribution of the axons forming the anterior root, causes the boundary line between these two columns to become somewhat indefinite. Furthermore, as the cervical and upper thoracic segments of the cord show slight furrow-like depressions at the points of exit of the fibers of the anterior roots, the anterior funiculus seems to be composed of two fasciculi, namely, the anteromedian and the antero-lateral. A similar condition exists posteriorly, this funiculus appearing as the posteromedian and posterolateral fasciculi. The following subdivisions may easily be made out:

1. The *anterior funiculus* comprises the area between the anterior median fissure, and the anterior root. It is motor in its function and is divided into the:

(a) *Fasciculus cerebrospinalis anterior*, also known as Türck's column, or the direct (anterior) pyramidal tract. It lies next to the median fissure and extends downward as far as the mid-thoracic region. Its caliber decreases constantly, because the fibers composing it enter

¹ Von Bechterew, *Die Funktionen der Nervencentra*, Jena, 1908–1911, and Edinger, *Vergl. Anat. des Gehirns*, Leipzig, 1911.

the gray matter of the opposite side by way of the anterior white commissure. We shall see later on that these fibers arise in the motor cortex of the cerebrum (cells of Betz) of the same and opposite side, and are therefore descending in their character.

(b) *Fasciculus anterior proprius*, also called the anterior ground bundle or root zone. This column occupies the area next to the anterior root and extends throughout the cord. The fibers composing it are commissural in their character, i.e., they bring different segments of the gray matter into functional relation. This end they accomplish by passing to higher as well as to lower levels of the cord, where they reënter the gray matter and make connections with other cells.

2. The *lateral funiculus* embraces the white matter between the anterior and posterior roots and is composed of the:

(a) *Fasciculus cerebrospinalis lateralis*, also called the lateral or crossed pyramidal tract. It occupies the posterior area of this funiculus, but its position varies somewhat at different levels of the cord. In the lumbar region, it comes right to the surface, while in the cervical and thoracic regions it remains at some distance from it. It is covered here by a layer of fibers composing the *fasciculus cerebellospinalis*. Its fibers arise in the motor area of the cerebrum (cells of Betz), but cross to the opposite side of the body in the medulla. In their downward course through the cord they terminate successively at different levels of the gray matter so that the size of the entire column diminishes gradually from above downward.

(b) *Fasciculus spinocerebellaris*, also designated as the direct cerebellar or Flechsig's column. It lies externally to the crossed pyramidal tract. Its fibers take their origin in the cells of Clark's column. From here they pass obliquely outward and upward and finally terminate in the cerebellum, where they decussate in part in the superior vermiform lobe of this structure.

(c) *Fasciculus anterolateralis superficialis*, also known as Gower's tract. It occupies the external realm of the lateral funiculus in front of the crossed pyramidal tract and extends forward as far as the anterior roots. It begins in the lumbar segment and forms a compact strand through the entire cord. The largest number of its fibers arise in the opposite gray matter and cross the midline by way of the white commissure. The uncrossed fibers find their origin in relation with axons which have passed through the gray commissure and have come from cell-bodies in the gray matter of the opposite side. In the brain-stem this column divides into several groups of fibers which terminate in the reticular nuclei, the cortex of the cerebellum, the tectum, the substantia nigra and the thalamus.

(d) *Fasciculus lateralis proprius* or lateral ground bundle. This tract forms a narrow layer next to the external surface of the gray matter. It is believed to be composed of efferent and afferent fibers, the former being situated in front. Its function seems to be associative, because its fibers originate in cells of the spinal gray matter and terminate at levels above and below their points of origin.

3. The *posterior funiculus* comprises the white matter between the posterior median fissure and the posterior roots. It consists of the:

(a) *Fasciculus gracilis*, also called the column of Goll or the posteromedian tract. It is situated next to the posterior fissure and begins with the posterior root of the coccygeal nerve. Beginning at this level, it gradually increases in size owing to the acquisition of the root fibers of higher nerves of the same side. Above the fifth thoracic nerve it retains its caliber or becomes even somewhat smaller, because while it ceases here to receive root fibers, it continues to give off collaterals to the successive segments of the gray matter. It terminates in the nucleus funicularis gracilis of the medulla.

(b) *Fasciculus cuneatus*, also known as the column of Burdach or posterolateral tract. It lies next to the posterior horn and begins in the middle thoracic region. As it acquires new fibers constantly, its size increases from below upward until it terminates in the nucleus funicularis cuneatus of the medulla. Its fibers are derived from the successive posterior roots of the spinal nerves of the same side as well as

from cells of the corresponding gray matter. The latter are short fibers, *i.e.*, associative in their function, while the former belong to the projection system.

Classification of the Tracts of the Spinal Cord.—In accordance with the foregoing histological discussion, it will be seen that the

FIG. 304.—DIAGRAM SHOWING THE COURSE, ORIGIN AND TERMINATION OF THE FIBERS OF THE PRINCIPAL TRACTS OF THE WHITE MATTER OF THE SPINAL CORD.

Descending tracts: 1a, a fiber of the crossed pyramid or corticospinal tract; 1b, an uncrossed fiber of the pyramid or corticospinal tract passing to the lateral column of the same side; 2, a fiber of the ventral pyramid or cortico-spinal tract; 3, a fiber of the ventrolateral descending or pontospinal tract; 4, a fiber of the rubrospinal tract; 5, a fiber of the common tract. Ascending tracts: 6, a fiber of the dorsomesial spinobulbar tract; 7, fibers of the dorsolateral spinobulbar tract; 9, one belonging to the dorsal spinocerebellar; 10, a fiber of the ventral spinocerebellar tract. (*Quain, Elements of Anatomy.*)

different fasciculi of the spinal cord constitute different *descending* and *ascending* tracts. In this connection brief reference should also be made to a number of small and narrow tracts which have been

localized in these fasciculi at different levels of the cord. But, the origin and distribution of the latter are still rather obscure so that the following physiological classification must necessarily be subject to frequent revision.

1. *Descending Tracts.* (a) *Pyramidal tracts.*—We have previously seen that the fibers composing the direct (anterior) and crossed (lateral) pyramidal tracts, originate in the large cells of Betz of the motor areas of the cerebrum. Hence, an injury to these regions or a transverse division of these paths at a lower level must result in a downward degeneration of these tracts. It should be remembered, however, that by far the largest number of these fibers cross to the opposite side so that, say, the left cerebral hemisphere eventually obtains control over the musculature of the right side of the body, and *vice versa*. Only a few fibers remain on the same side, where they eventually enter the lateral column. The afore-said crossing is effected principally in the pyramidal decussation in the lower region of the medulla, but in part also in the spinal cord itself. Thus, it appears that the crossed pyramidal tract is made up of fibers which have gained the opposite side in the medulla, while the anterior pyramidal tract comprises in addition a certain number of fibers which have failed to cross in the medulla but which seek the opposite side gradually by way of the anterior commissure. As this crossing is completed in the mid-dorsal region, these anterior tracts disappear at this level. In fact, it is said that they are entirely wanting in about 15 per cent. of human spinal cords, because in these cases the decussation is had solely in the medulla, the fibers being distributed from here exclusively to the crossed pyramidal tract.¹ This condition also prevails in the cat, while in the mole the fibers remain uncrossed and descend anteriorly. In the frog this system is absent.

It may be concluded, therefore, that the pyramidal tracts are efferent in their nature and form the motor path for those impulses which originate in the motor cells of the cerebrum and are finally transferred to the large motor neurons in the anterior horn of the spinal gray matter, whence they are distributed to the skeletal musculature. From this discussion it may be inferred that they are the chief constituents of the efferent side of the cerebral projection system. Hence, any injury to this path must result in a loss of voluntary control over the action of the corresponding skeletal muscles, but naturally, the ordinary reflex movements of the cord are not interfered with unless the lesion is situated at a low level. High lesions of the pyramidal system, as has been stated above, really tend to exaggerate the activity

FIG. 305.—SCHEMA REPRESENTING THE COURSE OF THE FIBERS OF THE PYRAMIDAL SYSTEM.

1, Fibers to the nuclei of the cranial nerve; 2, uncrossed fibers to the lateral pyramidal fasciculus; 3, fibers to the anterior pyramidal fasciculus crossing in the cord; 4 and 5, fibers that cross in the pyramidal decussation to make the lateral pyramidal tract of the opposite side. (Howell.)

¹Simpson, Quart. Jour. of Exp. Physiol., viii, 1914, 79; also: Lenhossek, Bau des Nervensystemes, 1895.

of the spinal cord. It is to be noted, however, that these defects differ in different animals in accordance with the state of development of these tracts. They are most apparent in the apes and man and less evident in lower animals, in which the pyramidal system is always rather incomplete. In the latter, other motor paths serve to bring the spinal nuclei into unison with the higher centers. This is also true of the dog, because the division of the pyramids causes merely a partial paralysis of the muscles, and still permits the stimulation of the cerebral cortex to evoke certain movements.¹ Clearly, therefore, the results obtained by experiments upon lower animals cannot be directly applied to man.

(b) The *anterior tectospinal bundle*, or *Held's bundle*, lies just beside the entrance to the anterior median fissure. It has its origin in the superior quadrigeminal colliculus and descends through the dorsal tegmented decussation, midbrain, pons and upper half of the medulla to a place between the pyramidal decussation and the isolated head of the anterior column. It is concerned with the production of the ocular and pupillary reflexes, of which circuits it forms the central division.

(c) The *rubrospinal* or *prepyramidal tract*, also called *Monakow's bundle*. It is triangular in outline and is situated anterior to the crossed pyramidal tract. Its fibers may be traced from the red nucleus, a group of cells situated in the midbrain anterior to the nucleus of the third nerve. Shortly after their origin they cross the midline of the body and descend through the pons, medulla and cord to the level of the lumbar region, where they arborize around the cells of the posterior extent of the anterior horn. This tract appears to be an adjunct of the pyramidal system, because the red nucleus is connected with the cerebrum and cerebellum.

(d) The *vestibulospinal tract* is composed of descending fibers which are scattered through the anterior funiculus in the immediate vicinity of the root fibers. They arise in the lateral vestibular nucleus (Deiters') in the medulla and terminate in the spinal gray matter. It may be inferred, therefore, that this tract constitutes an important transmitting system between the cerebellum and the cord, being directly concerned with the adjustment of the musculature to sensory stimuli from the semicircular canals.

(e) The *olivospinal tract* or *bundle of Helweg*. It is a small tract and is situated near the surface of the cord just lateral to the anterior roots. Its fibers are said to arise in the thalamus and to extend through the inferior olive of the medulla as far as the lower cervical region.

(f) The *comma tract* of *Schultze* is situated in the posterior funiculus of the cervical and upper thoracic regions. It occupies the anterior realm of the column of Burdach, and appears to be formed by the descending branches of the posterior root fibers. Many of the latter divide into ascending and descending branches and thus connect afferently with different levels of the cord. For this reason, they cannot be regarded as forming true descending tracts. A similar origin is ascribed to *Lissauer's bundle* which embraces the tip of the posterior horn, as well as to the oval field of *Flechsig* and the median triangle of *Gombault* and *Philippe*.

(g) The *septomarginal bundle* is oval in shape and borders upon the posterior median fissure. It contains short fibers, but has been said to embrace also certain fibers from the midbrain.

2. *Ascending Tracts*.—(a) The *posterior tracts* occupy the fasciculi gracilis and cuneatus, and are formed almost wholly by the axones of the cells situated in the ganglia of the spinal roots. Several of them also arise from different segments of the spinal gray matter. The former are characterized as exogenous and the latter as endogenous; moreover, while some of these fibers terminate at different levels of the gray matter, others extend through the entire length of these columns and eventually end in the nucleus gracilis and nucleus cuneatus of the medulla. The former, very clearly, are spinal associative in their function, while the latter belong to the projection system and form a part of the afferent side of this cerebral conducting path. During their course through the cord, these fibers remain on the side

¹ Rothmann, Zeitschr. f. klin. Med., xlviii, and Schäfer, Quart. Jour. of Exp. Physiol., iii, 1910, 355.

on which they have arisen, but finally cross the median line by way of the sensory decussation of the medulla. It is also to be noted that the fibers which have their origin at a low level, are gradually pushed toward the median fissure by those fibers which enter at higher levels, and naturally, as this displacement affects the exogenous fibers only, the upper thoracic and cervical segments of the fasciculus gracilis gradually assume the character of the conducting path for the root fibers of the lumbar and sacral regions.

FIG. 306.—DIAGRAM OF THE CHIEF CONNECTIONS BETWEEN THE SPINAL CORD AND THE CEREBRAL CORTX.

The spinal lemniscus complex carries the ascending exteroceptive systems (touch, temperature, and pain); the dorsal funiculus and medial lemniscus complex carry chiefly ascending proprioceptive impulses (a nerve of muscle sense is the only member of this group included in the drawing). The diagram also shows the sensory path from the skin of the head to the cerebral cortex through the V cranial nerve (trigeminal) and the trigeminal lemniscus. The pyramidal tract (tractus corticospinalis) is the common descending motor path for both exteroceptive and proprioceptive nervous impulses from the cerebral cortex. (Herrick.)

(b) The *direct or spinocerebellar tract* (Flechsig's) is one of the two best known tracts in the lateral funiculus. As its fibers arise in the cells of Clark's column, they are endogenous in character, and serve for the inward conduction of those impulses which have attained the aforesaid cells by way of certain fibers of the posterior root. While most of them enter the inferior peduncle of the cerebellum and terminate in the posterior and median areas of the vermiform lobe, some also

pass into the gray matter of the upper spinal cord. The cerebellar groups remain largely uncrossed.

(c) The *superficial anterolateral tract* (Gower's).—The origin of these fibers in the lower spinal gray matter and their distribution to the cerebellum and related parts suggest that they convey afferent impulses from the posterior roots to the cerebellum,¹ and hence, their function must be similar to that of the fibers of Flechsig's tract. They are concerned with the coördination of muscular movements, their immediate purpose being to aid in the conduction of the impulses from the receptors in the muscles, tendons and joints to the coördinating organ, the cere-

FIG. 307.—DIAGRAM OF THE SPINOCEREBELLAR, BULBOTEGMENTAL, CEREBELLOTEGMENTAL, PONTOTEGMENTAL, AND PONTOCEREBELLAR TRACTS.

OT, Optic thalamus; F, fillet; RN, red nucleus. (After v. Gehuchten.)

bellum. For this reason, they may be regarded as forming a part of the afferent arc required for the production of the muscle sense and coördination of muscular action. That this is true may also be gathered from the fact that the division of this tract is followed by a moderate degree of atonia and ataxia² below the seat of the lesion.

(d) The *spinothalamic* and *spinothalamic* tracts are really a part of Gower's tract. These fibers traverse the medulla and pons and terminate very largely in the optic

¹ Bruce, Quart. Jour. of Exp. Physiol., iii, 1910, 391; also see: Lewandowsky, Untersuchungen über die Leitungsbahnen d. Truncus cerebri, etc., Jena, 1904.

² Bing, Archiv für Physiol., 1906, 250; also see: Horsley and Macnalty, Brain, 1909, 237.

thalamus of the same side but in part also in the corpora quadrigemina of both sides.

(e) A few *scattered bundles* of ascending fibers are also found in the anterior funiculus. They intermingle here with the descending tracts mentioned previously. The fasciculi proprii or ground bundles are not mentioned separately in this enumeration, because parts of them have already been described under the heading of the septomarginal and comma tracts.

The Function of the Roots of the Spinal Cord. The Bell-Magendie Law.¹—The general conclusion to be derived from the preceding discussion is that the white matter of the spinal cord of the higher animals is arranged in definite tracts which connect:

(a) Different segments of this structure with one another, thus forming the propriospinal paths, *i.e.*, a short or reflex system of conduction.

(b) The cord with the hindbrain, midbrain and forebrain, forming a long or projection system of conduction. With the hindbrain the connections are made over the posterior cerebellar tracts, the tracts of Goll and Burdach, the spino-olivary and vestibulospinal bundles. The midbrain receives its impulses by way of the spinotectal tracts and discharges them over the rubrospinal. The forebrain (thalamus) is entered through the spinothalamic tracts. From here the impulses are relegated to the cerebrum, which organ, as has been stated above, is not in direct afferent communication with the cord, because the impulses directed to it from the latter structure, are first relayed into lower nuclei and centers before they are finally distributed to the cerebral cortex. On the efferent side, however, the cerebrum is in possession of a direct path in the shape of the anterior and lateral pyramidal tracts. As has been emphasized repeatedly, the mere entrance of an impulse into the cerebrum does not admit it to consciousness; in fact, many of the reactions resulting in consequence of cerebral activity retain their reflex character as strictly as those evoked exclusively with the help of the spinal cord. It is true, however, that many of them are controlled by consciousness. They are then converted into volitional acts, the preceding afferent impulses having been received in consciousness as sensations of different qualities.

We are now in a position to go one step farther and to inquire how the different spinal tracts and especially those belonging to the projection system, are connected with the distant receptors and effectors. It will be remembered that each spinal nerve arises by two roots, an anterior or ventral, and a posterior or dorsal, and that these roots finally unite to form a nerve. Centrally to their point of union, the posterior group of fibers is associated with a colony of cells, which form the so-called intervertebral ganglion. In 1811 Ch. Bell² found that the mechanical stimulation of the anterior group of fibers gives rise to movements, while the posterior behaves negatively in this

¹ Longet, *Anat. et physiol. de la syst. nerv.*, 1847.

² An idea of a new anatomy of the brain, London, 1811.

regard. In 1822 Magendie¹ succeeded in demonstrating that the division of the anterior roots destroys motion, while the section of the posterior roots produces a loss of sensation. Owing, however, to the fact that the former is in possession of a perfectly local system of sensory fibers and that the latter is connected with motor reflex paths, this investigator did not succeed in fully establishing their function. This end was finally attained by Joh. v. Müller as a result of his experiments upon the spinal roots of the frog.

In its modern form the Bell-Magendie law holds that the afferent impulses from the superficial and deep parts of the trunk and extremities are conducted into the cord by way of the posterior roots, while the efferent impulses to these parts leave this structure over the fibers of the anterior roots. Thus, a most perfect localization of sensory and motor function is had in this region of the nervous system. To prove this, we may resort to the methods of division and stimulation, as follows:

1. Section:

(A) Anterior root: loss of motion in the regions supplied by this nerve.

(B) Posterior root: loss of sensation (contralateral) in the region innervated by this nerve (ataxia and loss of reflex movements).

2. Stimulation:

(A) Anterior root:

(a) Distal end: motor results of the kind ordinarily produced by this nerve.

(b) Central end: no motor results, but retrogressive sensation.

(B) Posterior root:

(a) Distal end: no results.

(b) Central end: sensations of the kind ordinarily conveyed by this nerve.

In its complete form the Bell-Magendie law also takes cognizance of certain minor facts which are as follows: It has been mentioned above that the anterior root as such is not devoid of sensation and hence, does not differ in this regard from other tissues. For this reason its excitation must give rise to "retrogressive" sensory impulses which are purely local in their origin, and should therefore be sharply differentiated from those which arise at the periphery and attain consciousness by way of the posterior group of fibers.² In the second place, as the sensory impulses traversing the posterior roots also include those which help in the formation of the muscle-sense, the division of these fibers must necessarily be followed by a certain degree of ataxia; in other words, in the absence of the sensory impressions from the muscles and tendons, the muscular movements must lose their coördinated character. In the third place, it should be remembered that the stimulation of the central end of the divided posterior root may also give rise to movements, but these occasional motor effects are reflex in their nature and cease immediately after the division of the anterior roots. Being desirous of simplifying this topic as much as possible, I refrain at this time from a discussion of certain

¹ Jour. de Physiol., ii, 1822, 276.

² Cl. Bernard, Leçons sur la physiol. et la path. du syst. nerveux, i.

other facts which, however, do not put the general applicability of this law in question. I also omit for the present the structural and functional relationship existing between the spinal cord and the sympathetic system. We shall see later on that the anterior roots also contain efferent fibers for the autonomic organs and that these in turn send impulses to central parts by way of the rami communicantes and the posterior roots.

The Trophic Function of the Spinal Cord. The Wallerian Law of Degeneration.—It has been discovered by Nasse¹ that a nerve-fiber, when disconnected from its cell-body, undergoes certain very characteristic alterations in its structure. In applying this fact to

FIG. 308.

FIG. 308.—SCHEMA TO SHOW THE COURSE OF THE DEGENERATION FOLLOWING THE DIVISION OF THE ROOTS OF THE SPINAL CORD.

A, Division of the anterior root; B, division of the posterior root distally to spinal ganglion; C, division of the posterior root centrally to spinal ganglion. The degenerated portions are indicated in solid black.

FIG. 309.

FIG. 309.—SCHEMA ILLUSTRATING THE COURSE OF DEGENERATION IN MOTOR AND SENSORY NEURONS.

A, Motor neuron of the anterior root; B and C, sensory neurons of the posterior root. The portion separated from the cell degenerates, as is indicated by the dotted lines.

the spinal nerves, A. Waller² succeeded in demonstrating that a cut made distally to the intervertebral ganglion, leads to a degeneration of both roots in an outward direction, involving finally the entire nerve as far as its end-organs (secondary degeneration). Quite similarly, it was shown that the division of the spinal roots centrally to this ganglion gives rise to degenerative changes which pursue a course in opposite directions from the seat of the lesion, *i.e.*, the anterior root degenerates toward the periphery and the posterior

¹ Müller's Archiv, 1839, 405.

² Compt. rend., Acad. des sciences, xxxiv, 1852.

root toward the cord. The deduction immediately to be derived from these facts, is that the trophic center (cell-bodies) of the fibers composing the former, is situated in the spinal cord, while that of the posterior root fibers lies in the ganglion with which this root is associated. Having been told previously that the efferent fibers composing the anterior root originate in the ganglion cells of the gray matter of the anterior horn, and that the afferent fibers of the posterior root are derived from the cells of the spinal ganglia, we are now able to localize the degeneration in these neurons in the manner indicated by Fig. 309. It might be mentioned that the descending type of degeneration, observed in anterior poliomyelitis, is represented by neuron *A* of this figure, because it is commonly accepted that the active agent of this disease destroys the cells of the anterior horn, and thus produces a functional uselessness of the corresponding nerve fibers and motor organ. A degeneration very similar to that represented by neuron *C*, occurs in the course of *tabes dorsalis*, or *locomotor ataxia*. In this disease the lesion remains localized at first in the terminals of the posterior root fibers with the result that the muscle and tendon sense is rendered defective, thereby preventing the proper coördination of muscular movements.

These facts, however, do not justify us in recognizing the existence of special neurons with an exclusive trophic function, because the nutrition of a tissue is dependent primarily upon its activity, and the latter in turn upon the excitatory and regulatory power of the nerve cells. Thus, an injury to these nervous elements invariably leads to trophic disturbances in the tissues even without their being equipped with special trophic qualities. For this reason, we find that the skeletal muscles atrophy when separated from their ganglion cells. Exceptions to this rule are few in number and are referable to the fact that some muscles, such as the sphincter ani, are not under the direct control of the central nervous system. Upon this basis, we are also able to explain the trophic disturbances which are frequently observed in the course of degenerating afferent nerves (Fig. 309, *B*). Thus it is found that the inflammation of the ganglia upon the posterior roots leads to the condition of herpes zoster ("shingles") in the area from which the corresponding fibers are derived.¹ The skin may also become glossy and desquamate, which condition may eventually give rise to a loss of the hair and nails, or to a formation of ulcers. Inclusive of this trophic influence, the functions of the spinal cord may therefore be summarized as follows:

- (a) It is an important seat of reflex action.
- (b) It forms one of the principal conducting paths.
- (c) Its centers are automatically active and give rise to the tonicity of the musculature.
- (d) It regulates the activity and trophic condition of the tissues and plays an important part in the heat production of our body.

¹ Head and Campbell, *Pathology of Herpes Zoster*, Brain, xxiii, 1901, 353.

The Distribution of the Impulses Derived from the Posterior Roots.—The posterior roots of the cord are very important “feeders” of the central nervous system. Together with the afferent fibers of the cranial nerves, they constitute the only means by which the higher centers may be influenced by impulses generated peripherally. These impulses embrace first of all the superficial and deep sensations of touch, pain and temperature, as well as those derived from the receptors in the muscles and tendons, having to do with the muscle-sense. On their arrival in the terminals of the posterior root fibers,

Homolateral impulses underlying muscular sensibility—i.e. sense of passive position and of movement, also of touch and pressure for a few segments.

FIG. 310.—DIAGRAM TO ILLUSTRATE THE TERMINATION OF PERIPHERAL AFFERENT FIBERS IN THE SPINAL CORD, AND THE ORIGIN OF THE SECONDARY CENTRAL PATHS, WITH A BRIEF SUMMARY OF THEIR FUNCTION.

1, Bundles of fibers passing up in the posterior column—many myelopetal (to sp. cord) and the remainder bulbopetal (to p. col. nuclei); 2, fibers terminating around the cells of Clarke's column; 3, fibers arborizing around cells in the posterior horn, and intermediate gray matter; 4, ditto around the anterior horn-cells; 5, ditto swerving into the lateral column to neighboring gray matter; 6, direct, or dorsal spinocerebellar tract; 7 and 8, Gowers' tract, i.e. (7) ventral spinocerebellar tract; (8) spinothalamic and tectal tracts; 9, ascending tract in the anterior column. (*Starling after W. Page, May.*)

they are distributed to those particular groups of cells and fibers which are directly concerned with their conduction to other parts. Their distribution is effected as follows:

(A) *Impulses Retained at the Level of their Entrance into the Cord.*—They are reflex in their nature and gain the corresponding effector by way of the anterior root fibers. This transfer of the afferent impulses into efferent ones is accomplished directly through the intervention of the cells of the anterior and lateral horns of the neighboring gray matter. While the largest number of these impulses remain confined to the same side of the cord, some also seek the opposite spinal gray matter and opposite anterior root by way of the posterior white commissure.

(B) *Impulses Seeking Levels above and below their Level of Entrance.*—They are distributed to:

(a) *Higher or Lower Segments of the Cord.*—These are also reflex in character, but involve the spinal gray matter and anterior roots of segments situated above or below the point of their entrance. These segments are reached over the fibers of the ground bundles or by way of the terminals and collaterals of the fibers of the posterior columns. In the latter case, they are not relayed, because many of the fibers of the posterior roots divide inside the cord into an upper and a lower branch, the former eventually arborizing at a higher and the latter at a lower level than their point of bifurcation. The connection between the terminals of this afferent fiber and the anterior gray matter is effected in either case in the manner just described.

(b) *Higher Centers in the Cerebellum and Cerebrum.*—The cerebellar impulses are concerned with the muscle-sense and the coördination of muscular movements. They are transferred from the posterior root to posterior cells and subsequently to the cerebellar tracts in the lateral funiculus and the cerebellum. Some of these are no doubt transferred directly to efferent channels, while others pass from this organ to the cerebrum, where they may either enter consciousness or remain subconscious. They then seek the efferent tracts by way of the motor areas. The cerebral impulses leave the fibers of the posterior roots and enter either the posterior tracts or those of the lateral funiculus. Inasmuch as no separate tract is set aside for them by means of which they could reach the cerebrum directly, they are relayed in the medulla and basal ganglia to secondary bundles of fibers. These impulses serve conscious and subconscious reactions. In the first instance, they enter consciousness as sensations of touch, pain and temperature.

Nothing further need be said regarding the afferent impulses of touch, pain and temperature, when concerned with reflex action. Their course has been mapped out above under the headings of *A* and *B, a*. Much controversy, however, has arisen as to their course when they enter consciousness, and give rise to their respective sensations which are then followed by voluntary reactions. This controversy finds its origin in the diversity of the symptoms following lesions of the posterior and lateral fasciculi. Thus, it has been observed that the posterior tracts may be divided in lower animals without destroying the sense of touch. Cases have also been recorded of persons with extensive lesions of the same columns whose sense of touch was not seriously impaired. But this evidence does not prove that the tactile impulses do not enter the posterior tracts at all, but merely suggests that two paths are open to them, namely, the long projection fibers of the posterior funiculus and the short fibers of the lateral funiculus. Thus, if the former fibers are destroyed, these impulses are still able to gain the cerebrum by way of the latter. This view, however, is not fully in accord with the results of experiments upon lower animals, but is in agreement with the symptoms presented by persons suffering from certain affections of the spinal cord. While this matter cannot be definitely decided at the present time, it appears that these differences are chiefly dependent upon the fact that the spinal paths vary somewhat even among the mammals.

If we confine ourselves to man, we may draw the conclusion that the impulses of touch and pressure are transmitted under normal conditions to the posterior tracts of the same side, but may be transferred in the upper cord to the opposite anterolateral columns. Head

and Thompson¹ have elucidated this matter further by dividing the sense of touch into *tactile discrimination* and *tactile localization*. The former term is employed to designate the ability of being able to discriminate between two mechanical stimuli applied simultaneously to the skin. This sensation may be evoked most easily by touching the integument with a compass the points of which have been separated from one another. Tactile localization is the ability accurately to designate the area which has been stimulated. In certain spinal diseases, these two forms of touch sensation have been found to be dissociated. The former was lost, while the latter persisted. In explanation of this phenomenon, it is held that the fibers allotted to touch discrimination, are contained in the posterior tracts of the same side, while those conveying the impulses of touch proper, are included in the anterolateral fasciculi and cross the median line below the medulla.

In addition to this dissociation of the tactile impressions into touch discrimination and touch localization, the cutaneous sensations may also be divided into two groups, namely, those of touch and those of pain and temperature. The former impulses, as we have just seen, select in part the posterior columns, while the latter appear to enter the cells of the posterior gray matter, whence they attain the tracts of the opposite anterolateral fasciculi. The evidence which may be submitted in support of this view, is the fact that in syringomyelia the sensations of touch and pressure are retained, while those of pain and temperature are lost. In other words, the patient exhibits an analgesia and thermo-anesthesia below the seat of the lesion. These symptoms are suggestive, because this disease affects chiefly the gray matter of the cord, causing a vacuolization of the cells and, therefore, a destruction of the connection between the posterior roots and the anterolateral fasciculi of the same and opposite sides. It would seem, therefore, that the loss of the sensations of pain and temperature is dependent in this case upon the fact that they cannot reach their destination on account of this block upon the path usually selected by them in gaining the opposite anterolateral tract.

The impulses serving the muscle-sense, may also be divided into two groups, namely, those which pass directly to the cerebellum and always remain subconscious and those which are relayed to the cerebrum and finally involve volition. It has been stated above that the former select the anterior and posterior cerebellar tracts of the lateral funiculus of the same side, while the latter ascend in the posterior columns of the same side. The latter, however, cross finally to the opposite cerebral hemisphere by way of the optic thalamus. Our muscular movements are executed in accordance with the character of the impulses received from our muscles and tendons. This regulation is primarily cerebellar, but may be modified by volition, *i.e.*, the activity of our muscles may be controlled by the cerebellum and cerebrum

¹ Brain, 1906; also see: Saunders, Brain, xxxvi, 1913, 166.

either without or with the help of consciousness, especially of volition. In the first case, the control is involuntary or reflex, and in the second, volitional and based upon an accurate conception in consciousness of the state of contraction of our muscles and of the position of our limbs.

The Effects of Hemisection of the Spinal Cord.—The symptoms following the division of one-half of the spinal cord, are homolateral and contralateral in their nature, *i.e.*, they may or may not be confined to the side of the lesion.

A. Homolateral:

- (a) Motor paralysis, affecting (a) the skeletal muscles innervated by the efferent fibers which leave the cord below the level of the section, and (b) the smooth musculature of the blood-vessels. The latter is made evident by the injection of the blood-vessels of the parts affected and the consequent rise in temperature. The skin becomes dry which fact points toward a secretory motor paralysis.
- (b) Sensory paralysis (anesthesia) in the region of those afferent fibers which enter directly at the seat of the injury. This zone is, of course, limited. Loss of the muscle-sense and tactile discrimination. The other parts show a certain degree of hyperesthesia.

B. Contralateral:

- (a) Motor paralysis, negative.
- (b) Sensory paralysis, affecting pain, temperature and tactile localization in the region innervated by those fibers which have crossed below the level of the lesion.

This syndrome, consisting of unilateral loss of motion and contralateral loss of sensation, is not very evident in the lower animals, but this need not surprise us, because the localization of conduction in the simple spinal cords differs somewhat from that found in the human cord.² In addition, we are confronted here by the difficulty that an animal cannot interpret sensory disturbances for us.

¹ Brown-Séquard, *Jour. de Physiol.*, vi, 1863, 124; also see: Petrén, *Archiv für Psychiatrie*, xlvii, 1911, 495.

² Karpus and Kreidl, *Pföger's Archiv*, clviii, 1914, 275.

SECTION XVI

THE AUTONOMIC NERVOUS SYSTEM

CHAPTER LI

THE SYMPATHETIC AND PARASYMPATHETIC SYSTEMS

General Arrangement.—It has been stated above that the nervous system consists of a central and a peripheral division, and that the latter in turn is built up of (a) the cranial and spinal nerves, and (b) the ganglia and nerves of the sympathetic system. The term sympathetic, however, is somewhat misleading, because, as originally employed, this system included merely those ganglia which are situated along the spinal cord, beginning above with the superior cervical and ending below with the coccygeal. Its function was said to be the regulation of the activities of the internal organs or viscera. In the course of time a number of ganglia have also been found which, although innervating the viscera, do not occupy a position within the realm of the sympathetic system as originally mapped out. These are said to form the so-called parasympathetic system. On account of this conflict, Langley¹ has advocated the use of the more general term visceral or autonomic. Hence, in its modern conception the autonomic nervous system is composed of a number of ganglia and plexuses of nerves which are rather sharply differentiated from the cerebrospinal system by certain anatomical, histological and physiological characteristics. It is formed, on the one hand, by the sympathetic system as originally conceived and, on the other, by certain ganglia which are situated in the realm of the cranial and sacral nerves. The latter are collectively known as the parasympathetic system. In making these distinctions the student is cautioned not to regard the autonomic system as a functional curiosity, or to separate it completely from the cerebrospinal system, because it forms after all a closely correlated division of the whole nervous mechanism.

The entire autonomic nervous system is composed of a series of ganglia which are scattered through the regions of the head, neck, thorax, abdomen and pelvis, beginning above with the superior cervical and terminating below with the coccygeal ganglion. These colonies of cells are united by nerve-fibers which are frequently augmented into networks or plexuses. It consists of:

¹ *Ergebn. der Physiol.*, ii, 1903, 2, and *Zentralbl. für Physiol.*, xxvii, 1913, 149.

FIG. 311.—DIAGRAMMATIC OUTLINE OF THE AUTONOMIC SYSTEM. (After Meyer and Gollietz.)

- A. The *sympathetic chain*, situated on each side of the vertebral column and consisting of ganglia which are connected by strands of fibers. It is divided into a:
- (a) *Cervical portion* which is placed along the neck and is beset with the superior, middle and inferior cervical ganglia. This delicate string of non-médullated fibers may pursue an independent course along the carotid artery (rabbit) or be intermingled with the médullated fibers of the vagus (dog).
 - (b) *Thoracic portion*, consisting of eleven or twelve ganglia, the first three of which are united into the large ganglion stellatum.
 - (c) *Lumbar portion*, embracing the three or four ganglia of this region.
 - (d) *Sacrococcygeal portion*, formed by an equal number of sacral ganglia terminating with the ganglion coccygeum.
- B. A *system of large ganglia* which may be grouped as:
- (a) *Cranial*, for example, the ganglion ciliare upon the third nerve, the ganglion sphenopalatinum upon the second branch of the trigeminus, the ganglion oticum et ganglion submaxillare upon the third branch of the same nerve. The vagus and glossopharyngeus also embrace certain fibers which connect with the sympathetic system.
 - (b) *Thoracic*, for example, the plexus cardiacus upon the arch of the aorta.
 - (c) *Abdominal*, for example, the plexus solaris, embracing the right and left suprarenal, the superior mesenteric, the celiac and certain smaller ganglia in the region of the stomach. The greater and lesser splanchnic nerves unite this complex with the thoracic ganglia. The distalmost ramifications of the sympathetic system in this region form the plexuses of Meissner and Auerbach.
 - (d) *Pelvic*, for example, the ganglion hypogastricum.

Characteristics of the Autonomic Nervous System.—The preceding outline teaches us that the autonomic nervous system occupies an *anatomically* distinct position; in fact, its gross anatomical characteristics are such that we are tempted to regard it as a nervous system within a nervous system. On the *histological* side, we find that the sympathetic cells are usually multipolar, rounded in outline, and somewhat smaller than those belonging to the cerebrospinal structures. The nerve-fibers are characterized by an absence of the myelin sheath which imparts to them a grayish color. The only exception to this rule is to be found in the médullated fibers, forming the connection between the gray matter of the cerebrospinal system and the neighboring sympathetic ganglia. These bridges of fibers are known as the white rami communicantes. On the *physiological* side, we observe that the reactions occurring in the realm of the sympathetic system, are for the most part subconscious. This implies that they are not under the direct guidance of volition and are, therefore, typically reflex in their character. Besides, as they are relatively independent of the central nervous system, and may continue even after the destruction of the latter, they are usually described as autonomic. On the *pharmacological* side, we find that the sympathetic elements behave in a very characteristic manner toward certain drugs. Nicotin acts as a cell poison, *i.e.*, it paralyzes the synapses and thus separates the distal from the central neuron. Efferent impulses are in this way prevented from reaching the peripheral motor organ. Adrenalin exerts a specific action upon the thoracic and lumbar divisions of the sympathetic system, while atropin, muscarin and pilocarpin are said

to act primarily upon the parasympathetic system, and chiefly upon the cranial ganglia and their ramifications.

The Function of the Autonomic System.—The innervation of the striated musculature is effected by fibers which arise in the cerebrum, cerebellum and spinal cord and pursue a perfectly straight course to the periphery. Those fibers, on the other hand, which are concerned with the vegetative processes, do not pass directly to the motor end-organs, but are first relayed into the sympathetic system. The latter, therefore, may be regarded as a siding upon the cerebrospinal tract. In its amplified form this statement signifies that the impulses apportioned to striated muscle are distinctly cerebrospinal in their origin and remain so throughout their course, while those

FIG. 312.—CELLS FROM THE GANGL. CERVICALE SUPREMUM OF MAN.

A and B, Cells with short dendrites; C, cell with long dendrites; a, axon. (Cajal.)

distributed to smooth and cardiac muscle tissue, as well as to the glands, do not remain so, but presently assume the characteristics of the autonomic or sympathetic system. It has been stated above that the effectors are limited in number, because only two structural units enter into their formation, namely, muscle tissue and glandular tissue. The former, however, presents itself as striated, smooth and cardiac muscle. We now observe that the smooth and cardiac muscle tissues, together with the glandular tissue, form the typical motor organs of the autonomic system, while the striated muscle alone remains distinctly cerebrospinal in its character.

In further analysis of this fact it becomes immediately apparent

that the motor units of the autonomic system are moulded into an array of end-organs presenting a most perplexing structural and of functional diversity. Naturally, all of them are concerned with vegetative processes and as such give rise to movements as well as to secretions. The former embrace the musculomotor effects along the alimentary and urinary tracts, the vasomotor and pilomotor actions, the movements of the iris, and others. It would lead us altogether too far to discuss these different autonomic functions in detail; many of them, in fact, we have become acquainted with in the course of our studies upon respiration, the circulation of the blood and reflex action. For this reason, we shall confine ourselves at this time to a more general summary, such as the following:

A. The Cranial or Parasympathetic System.

- (a) The region of the midbrain. These fibers pass through the nervus oculomotorius and end in the gangl. ciliare. Motor fibers are sent to the musc. sphincter pupillæ and musc. ciliaris.
- (b) The region of the bulb. (1) The facial nerve conveys fibers to the gangl. sphenopalatinum (nerv. petrosus superf. major), whence they gain the mucous membrane of the nose, palate and upper pharynx as well as the lacrimal, submaxillary and sublingual glands. They are vasomotor and secretomotor in their function. (2) The glossopharyngeus contains fibers for the gangl. oticum (nerv. tympanicus et nerv. petrosus superf. minor), whence they gain the parotid gland. They are vasodilator and secretomotor in their function. (3) The vagus nerve embraces inhibitor fibers for the heart, motor fibers for the musculature of the bronchi, esophagus, stomach and intestine, and secretomotor fibers for the glands of the stomach and pancreas.

B. The Cervical Sympathetic System.

1. Musculomotor fibers for the musc. dilator pupillæ and the smooth muscle tissue of the orbits and eyelids.
2. Vasomotor fibers for the blood-vessels of the ears, face, conjunctiva, iris, choroidea, salivary glands, esophagus, larynx, thyroid, and brain.
3. Secretomotor fibers for the sweat glands of the head region, and the salivary and lacrimal glands.

C. The Thoracic Sympathetic System.

- (a) Vertebral ganglia:
 1. Vasomotor fibers for the skin of the trunk and extremities.
 2. Pilomotor fibers for the same regions.
 3. Secretomotor fibers for the sweat glands of the same areas.
- (b) Thoracic and abdominal ganglia:
 1. Musculomotor fibers for the heart (gangl. stellatum).
 2. Vasomotor fibers for the abdominal viscera (splanchnic system and solar ganglia).
 3. Vasomotor fibers for the colon descendens, rectum, bladder and uterus (gangl. mesent. inf. and nerv. hypogastrici).

D. The Sacral Sympathetic System (Parasympathetic in Character).

1. Musculomotor fibers for the colon descendens, rectum, bladder and genital organs.

The Connections between the Cerebrospinal and Autonomic Systems.—Inasmuch as the vegetative processes are under the direct control of the autonomic system, it must be evident that those impulses which are relegated to this system from the brain and cord,

must leave the cerebrospinal channels and enter the sympathetic ganglia. This transfer is accomplished in three different regions, namely, by way of the:

A. Cranial nerves.

(a) Midbrain, third nerve and *gangl. ciliare*.

(b) Bulb. (1) Second branch of the trigeminus, *gangl. sphenopalatinum*. (2) Third branch of the trigeminus and *gangl. oticum et gangl. submaxillare*.

(3) Vagus and glossopharyngeus.

B. Thoracic and lumbar divisions of the spinal cord, from the first thoracic to the fourth lumbar nerves.

C. Sacral division of the spinal cord, over the *nerv. pelvici*.

We have previously seen that the sympathetic system as originally described, consists of a chain of ganglia and their connections situated along the vertebral column in the region of the thoracic and lumbar segments of the spinal cord. But the autonomic system also includes a number of ganglia and plexuses which do not belong to this particular region of the nervous system, but form the anatomically distinct parasympathetic system. The latter embraces the cranial and sacral ganglia. To summarize, the autonomic nervous system consists of the sympathetic and parasympathetic systems. The latter includes all those ganglia and plexuses which are not directly related to the thoracic and lumbar divisions of the spinal cord. A glance at Fig. 311 will show that the largest number of the viscera receive a double nerve supply, namely, one from the sympathetic system proper and one from the parasympathetic system.¹ Peculiarly enough, the functions of these two groups of fibers are generally antagonistic to one another. In illustration of this statement might be mentioned the variations in the size of the pupil, or in the action of the heart. In the former case, the stimulation of the oculomotor nerve representing the autonomic pathway from the midbrain, gives pupillar constriction and the excitation of the cervical sympathetic, pupillar dilatation. In the case of the heart, the bulbar autonomic fibers contained in the vagus nerve, are cardio-inhibitory in their function, and the sympathetic, cardio-acceleratory.

Having found that the cerebrospinal and autonomic systems are connected by definite bridges of fibers, let us for a moment examine the structural details of one of these. I select for this purpose the spino sympathetic rami, because their course has been made out with at least a fair degree of accuracy (Fig. 313). We have seen that the axons of the cells in the anterior horn seek their corresponding motor end-organs by way of the anterior roots (I). In tracing these fibers outward to the point where they intermingle with the afferent fibers tending toward the posterior root, it is noted that a number of them leave the mixed nerve and pursue a straight course toward the sympathetic ganglion at the side of the vertebral column (II and III).

¹ Gottlieb and Meyer, *Die exper. Pharmak. als Grundlage der Arzneibehandlung*, Berlin, 1912.

These fibers retain their medullary sheath and form the so-called *ramus albus communicans* (*W*), *i.e.*, a bridge by means of which certain efferent cerebrospinal impulses are enabled to enter the sympathetic system (*S*). The cell-bodies of these neurons form the lateromedian group of cells of the anterior horn in the thoracic and lumbar regions of the spinal cord. It is to be noted, therefore, that the anterior root is made up of two groups of efferent fibers, one of which conveys impulses directly to the striated muscles and the other, to the sympathetic system. The former are musculomotor (striated muscle) in their function, and the latter, musculomotor (smooth muscle) vasomotor, secretomotor and pilomotor.

FIG. 313.—DIAGRAMMATIC REPRESENTATION OF THE CONNECTION BETWEEN THE CEREBRO-SPINAL AND SYMPATHETIC SYSTEMS.

AR and *PR*, Anterior and posterior roots of the spinal cord; *SG*, spinal ganglion; *N*, spinal nerve; *W*, white ramus; *G*, gray ramus; *S*, sympathetic ganglion; *I*, ordinary motor neuron, the axon of which pursues a straight course to peripheral effector; *II*, motor neuron, the axon of which enters sympathetic ganglion through the white ramus. *III*, secondary neuron carrying the impulses from *II* to other parts of sympathetic system; *IV*, secondary neuron; carrying impulses from sympathetic system through the gray ramus to the peripheral effector in the domain of the cerebrospinal system; *V*, neuron carrying afferent impulses from sympathetic system into cerebrospinal system by way of spinal ganglion and posterior root.

Immediately adjoining the *ramus albus* is another bridge which unites the sympathetic ganglion with a somewhat more peripheral point of the mixed nerve. Its gray color suggests that the fibers composing it are non-medullated and are, therefore, of sympathetic origin. This is the *ramus griseus communicans* (*G*). In some animals, however, the white and gray rami are united into a single trunk and arise from the same segment of the mixed nerve immediately beside the spinal ganglion. It need scarcely be emphasized that the gray ramus forms an afferent connection which enables sympathetic impulses to reach the spinocerebral tracts (*IV* and *V*).

At the hand of these details, we are now in a position to explain why typically autonomic functions may also be had in regions which on casual observation seem to be innervated exclusively by a cerebro-spinal nerve. Thus, we observe that vasomotor and secretomotor actions are not restricted to the viscera, but are also enacted in the integument and deeper structures of the trunk, arms and legs. It must be inferred, therefore, that the spinal nerves innervating these parts, derive their supply of sympathetic fibers by way of the gray rami (IV). In this way, their original power of regulating the activity of the striated musculature is augmented by the control of the smooth muscle and glandular tissue. To illustrate, the sciatic nerve contains first of all a certain number of fibers for the skeletal muscles of the leg, secondly, fibers for the smooth muscle of the blood-vessels (vasomotor) and skin (pilomotor) and thirdly, fibers for the sweat glands (secretomotor) of this part. The former pursue a straight course from the spinal cord to their peripheral effectors (I), while the latter are first diverted into the sympathetic ganglia by way of the white rami (II), whence they are again directed into this spinal nerve by way of the gray rami (IV). For this reason, they are frequently designated as recurrent fibers. It seems quite probable that a similar arrangement exists at the points of union between the cranial nerves and the sympathetic, or more correctly speaking, the parasympathetic system.

The peculiar manner of distribution of these fibers is well illustrated by that of the pilomotors.¹ Using the cat as an example, it is found that the latter leave the spinal gray matter by way of the anterior roots of the fourth thoracic to third lumbar nerve. They enter the sympathetic system through the white rami, where they arborize in the ganglia of this chain to form connections with neighboring ganglia above and below their point of entrance. Each ganglion in turn remits a certain number of secondary fibers which again reach the corresponding spinal nerve by way of the neighboring gray ramus. From here they are distributed to the smooth muscle cells of the skin of that particular region. The fact that the sympathetic ganglia permit of a spreading of the primary impulse may be proved by the stimulation of the neighboring white and gray rami. For example, while the excitation of a certain gray ramus will yield pilomotor effects only in that segment of the body to which the corresponding mixed nerve is distributed, the stimulation of the neighboring white ramus most generally evokes these effects in the areas of the three or four adjoining spinal nerves. Obviously, this result can only be obtained if the primary impulse is relayed to neighboring efferent paths, and naturally, there is every reason to believe that this spreading is not

¹ While the production of "goose flesh" and the erection of the hairs are usually classified as involuntary phenomena, cases have been placed on record which show that individuals may acquire an accurate voluntary control over these otherwise purely sympathetic reactions.

confined to the pilomotor impulses, but also involves other sympathetic impulses.

Afferent Conduction in the Autonomic System.—We have noted that those fibers of the anterior horn which eventually enter the white ramus communicans, terminate around the cells of the first sympathetic ganglion (Fig. 314, *S*). The axons of the latter either return to the spinal nerve by way of the gray ramus communicans or continue within this system to other more distant ganglia. The neuron forming the connection between the cord and the sympathetic ganglion constitutes the preganglionic path (*P*), and the one situated on the distal side of the ganglion, the postganglionic path (*Po*). This terminology, however, is not always indicative of real conditions, because some of the preganglionic fibers may pass directly through the first sympathetic ganglia without entering into communication by synapse with these cells. According to Langley, the precise nature of a certain sympathetic fiber may be ascertained by moistening the ganglion with a solution of nicotin (*N*). This agent, it will be remem-

FIG. 314.—DIAGRAM TO ILLUSTRATE THE ACTION OF NICOTIN.

C, Spinal cord; *P*, preganglionic path; *S*, sympathetic ganglion; *Po*, postganglionic path; *E*, effector; *I*, neuron which does not form a synapse in *S*; *II*, neuron forming synapse in *S*; *N*, destroys connections in synapse, blocking nerve impulse in neuron *II* but not in *I*.

bered, first stimulates and then paralyzes the cells, preëminently at their junction with the axon terminations of the central neurons. Consequently, the stimulation of the preganglionic path must remain without effect if the fibers composing the latter actually enter into synapses within the nicotinized area (*II*). The reason for this is that the nicotin has produced a block within the ganglion. Conversely, if the central fibers traverse the ganglion without entering into communication with other cells (*I*), they must necessarily retain their power of conducting impulses to peripheral parts, because the nicotin does not affect the nerve-fibers. In the latter case, therefore, the excitation of the preganglionic path must give rise to motor effects. It is true, however, that this method does not allow of a universal application, because certain animals, such as the dog, are very resistant against this agent; in fact, its action differs even in the same animal when applied to different structures. Thus, it has been found that the cervical ganglia are much more susceptible to it than the ganglia of the splanchnic area.

The autonomic nervous system is essentially a distributing mechanism and hence, its ganglia may be said to serve primarily the purpose

of relay centers. As such they effect a considerable increase in the number of the efferent channels, because when the prèganglionic path terminates in a certain sympathetic ganglion, its fibers arborize and form various new connections with these cells. The postganglionic path, therefore, must be numerically stronger than the preganglionic. A similar multiplication of paths results in the next ganglion and so on until the periphery has been reached, where we find such intricate ramifications of fibers as the plexuses of Meissner and Auerbach, or the plexus cardiacus. Obviously, this fan-like expansion of the primary path into multiple secondary and tertiary paths, enables the principal center to control a large number of effectors and a wide area of tissue. In the second place, it renders the distal ganglia and plexuses partially independent of the cerebrospinal centers, because they can intercommunicate with one another without that the impulses need be relayed within the cerebrospinal system.

The formation of these relatively local centers for the control of particular processes, necessitates the development of a certain number of afferent channels, without which the motor actions could not attain the preciseness required of them. While it cannot be doubted that these afferent elements are present, it must be admitted that they are fewer in number and retain for the most part a local importance. It is also evident that their number varies considerably in different parts of the autonomic system. This must necessarily be so because certain structures, such as the glands along the intestinal tract, require a closer functional correlation than other organs. In general, it may be said that these afferent sympathetic neurons serve two purposes, namely, to effect perfectly local reflexes and to consummate reactions in parts remote from the seat of the stimulation. In the latter case, the impulses may even enter consciousness and give rise to voluntary actions. This, however, is rather the exception. To illustrate, the stomach or intestine may be excised and if kept under proper conditions of moisture and temperature, may be made to move and to secrete in a manner not widely different from normal. This implies that these organs are in possession of local nervous mechanisms, consisting of afferent and efferent arcs and their corresponding end-organs, which enable them to continue their actions even when isolated from the cerebrospinal system or from neighboring sympathetic ganglia. But it is also evident that these organs are constantly subjected to stimuli arising elsewhere in the autonomic system or even in the cerebrospinal system itself. Thus, a flow of gastric juice or of any other digestive secretion may be evoked by stimuli arising elsewhere in the abdominal cavity or in the receptors of the mucous membrane of the mouth, the taste-buds, olfactory cells, and others. The fact that the different sympathetic paths contain afferent fibers, finds ample proof in the pressor and depressor reactions following in the wake of the excitation of the hepatic and mesenteric plexuses.¹ It may be

¹ Burton-Opitz, *Quart. Jour. of Exp. Physiol.*; iv, 1911, 93.

concluded that these different local reflex circuits are associated by commissural fibers.¹

Lastly, it should be noted that the afferent impulses of the autonomic system may pass into the cerebrospinal system to be received eventually in consciousness (Fig. 314, V). The fact that a path of this kind exists, may be gathered from the work of Dogiel,² who has found that afferent visceral fibers arise in certain sensory cells of the sympathetic system which then enter the posterior root and arborize around the cells of the spinal ganglion. From here these visceral impulses are conveyed inward over the usual afferent tracts of the spinal cord. Thus we may obtain at times distinct sensations of visceral pressure, pain and temperature, such as arise in the course of the movements of the stomach, intestine, bladder, and other organs. It must be admitted, however, that the viscera are relatively insensitive to ordinary stimuli, as may be gathered from the fact that the handling or cutting of internal organs does not give rise to a decided sensation of pain, whereas the mere opening of a body-cavity by an incision through the integument can scarcely be effected without local or general anesthesia. It should be noted, however, that the sensation of visceral pain need not be restricted to the area in which it has been produced, but may also be projected to the surface layers of the body by way of the corresponding cutaneous somatic fibers. Thus, a diseased organ may give rise to a hypersensitiveness (hyperalgesia) and tenderness to mechanical and thermal stimuli in an area of the integument corresponding to the distribution of these fibers. As examples of referred visceral pain might be mentioned the radially disseminated pain experienced in the course of the passage of calculi through the biliary ducts or the extreme painful sensations which may be elicited by pressing upon the integument in the region of a gastric ulcer.

In general, therefore, it may be said that the autonomic system possesses the same functional powers as the cerebrospinal system, because it serves as a:

- (a) Conductor of efferent and afferent impulses,
- (b) Center for reflex action,
- (c) Tonically automatic center which retains the parts innervated by it in a condition of tonus, and as a
- (d) Center for the regulation of the trophic condition of these parts.

Pseudo- or Axon-reflexes.—The question has frequently been asked whether reflexes may also be elicited with the help of single ganglia and their peripheral connections? This should remind us first of all of the controversy pertaining to the nature of the patellar reflex which has finally been decided in favor of the view that it is not an axon-reflex, but is actually effected with the help of the corresponding spinal center. The only other structure which need be considered in this connection is the spinal ganglion. It has been found

¹ Hoffman, *Jahresber. für die ges. Med.*, cclxxi, 1904, 113.

² *Der Bau der Spinalganglien des Menschen und der Säugetiere*, Jena, 1908.

that, in the lower forms, its cells are typically bipolar, while in the mammals they are unipolar, possessing a single process which divides into two branches, one of which enters the spinal cord and the other, the spinal nerve. As commonly conceived, the function of these fibers is to conduct impulses from the periphery to the posterior region of the spinal cord. Naturally, the severance of the corresponding posterior root would render these fibers useless for reflex action, because they would thereby be disconnected from their efferent channels and motor-organs. A moment ago, however, we have noted that the

FIG. 315.—DIAGRAM SHOWING NERVOUS INNervation OF BLADDER.

C, Spinal cord; JM, inferior mesenteric ganglion; P, preganglionic path; Po, post-ganglionic path formed by H, the hypogastric nerves; B, bladder.

spinal ganglia receive certain afferent fibers from the sympathetic system. Under experimental conditions these afferent sympathetic fibers may also be made to conduct in a centrifugal or efferent direction. It need not surprise us, therefore, to learn that the stimulation of these spinal ganglia frequently gives rise to vasodilator effects in that region of the body from which the aforesaid afferent fibers have been derived. It is highly improbable that an effect of this kind is produced under normal conditions, although it may arise in consequence of inflammatory reactions in the region of the spinal ganglia, multiple neuritis and other conditions.

While our search for axon-reflexes within the realm of the cerebrospinal system has thus proved negative, it cannot be doubted that the ganglia of the autonomic system are well adapted for this form of reflex action, because practically every one of them is a reflex center dominating the function of a rather circumscribed region of the body. No definite facts, however, are at hand to prove that the sympathetic system is especially constructed for true axon-reflexes. The example usually given is the following: If the inferior mesenteric ganglion (Fig. 315) is isolated from the central nervous system by the division of its preganglionic path (P), but is left in functional relation with the bladder (B) through the two hypogastric nerves (H), the stimulation of the central end of one of these nerves invariably evokes a contraction of the musculature of the opposite half of this organ. If the aforesaid ganglion is now moistened with a solution of nicotin, this motor effect cannot be obtained. The conclusion to be derived from this experiment is that this "reflex" cannot be effected without the help of the cells of the inferior mesenteric ganglion, but since the normal conditions of conduction have been reversed in this case, we cannot justly regard this reaction as a true reflex. For this reason, Langley and Anderson¹ have applied to it the term of pseudo-

¹ Jour. of Physiol., xvi, 1894, 410.

or axon-reflex. Obviously, the stimulus is applied here to normally efferent fibers from which the impulse is then transferred at the central synapses to the efferent fibers of the opposite side. This transfer is made possible by the fact that each preganglionic fiber arriving in this ganglion, divides into two branches, one of which pursues a direct course to the corresponding side of the bladder, while the other makes connections by synapse with the fibers forming the opposite hypogastric nerve.

On closer analysis, however, it becomes evident that this particular experiment does not prove anything further than that the normal direction of conduction in the hypogastric fibers may be reversed by experimental means. This is not a new fact, because Kühne has shown that a similar reversion may be effected in the motor nerves of skeletal muscle. It will be remembered that the nerve innervating the gracilis muscle divides into two branches, one of which supplies the upper, and the other, the lower end of this muscle (Fig. 74). 'Inasmuch as a contraction may be evoked in its upper end by the stimulation of the nerve terminals in its lower end, the fibers of this normally efferent branch must be able to conduct the impulses so generated in an afferent direction. It should not be assumed, however, that this reversal of conduction may also take place under perfectly normal conditions. The same statement applies to the manner of conduction within the sympathetic system, because we have not been able to observe these phenomena under other than experimental conditions. There is one reaction, however, which may be of positive value and that is the following: If an irritant, such as mustard oil, is applied to the skin, this area becomes red, swollen, warm and painful in consequence of the dilatation of its blood-vessels. These changes may also be brought about after the sensory fibers from this region have been severed, but are much diminished if the sensitiveness in this part is first abolished by a local anesthetic. It appears, therefore, that this vasomotor reaction is not effected in a direct manner, but reflexly. Now, inasmuch as this area may be isolated from its center by the division of its afferent fibers, the resultant dilatation of the blood-vessels must have been brought about by a local reflex accomplished solely with the help of peripheral axons and their collaterals.¹

¹ Bardy, Skand. Archiv für Physiol., xxii, 1908, 194.

SECTION XVII

THE MEDULLA OBLONGATA AND THE CRANIAL NERVES

CHAPTER LII

THE FUNCTION OF THE MEDULLA OBLONGATA

The Medulla as a Reflex Center.—While the medulla oblongata or bulb may be regarded essentially as a part of the spinal cord, it really possesses a much greater functional importance than the latter, because it gives lodgment to a number of centers which control the most vital processes in our body. Thus, a separation may be effected

FIG. 316.—CROSS-SECTION THROUGH THE ADULT HUMAN MEDULLA OBLONGATA AT THE LEVEL OF THE IX CRANIAL NERVE. (From Cunningham's Anatomy.)

between this structure and the other parts of the central nervous system without actually destroying the life of the animal, but its isolation must be brought about by sections through the region of the pons and through the spinal cord below the nuclei of the phrenic nerves. If the latter section is made above this point, the ensuing paralysis of the diaphragm would, of course, make life impossible. Similarly,

the destruction of the medulla itself is followed by an almost immediate cessation of the respiratory movements, a relaxation of the vascular channels and a stoppage of the heart.

The centers situated in the domain of the bulb are of two kinds, namely, simple reflex and dominating or automatic. Regarding their function, nothing further need be said, because the manner in which reflex action is effected has already been discussed in detail in an earlier chapter. The following bulbar reflex centers have been localized with some degree of accuracy:

(a) Closure of the eyelids. The sensory impulses reach the medulla from the cornea, conjunctiva, and vicinity of the eyelids by way of the trigeminal nerve. They are transferred to the motor fibers of that branch of the facial nerve which innervates the orbicularis palpebrarum. The center itself extends from the alacina to the posterior border of the pons. While this reflex is bilateral in character, the volitional closure of the lids may be unilateral and may be intensified by the contraction of the neighboring muscles of the face.

(b) Center for sneezing. The afferent arc is formed by the trigeminal, and the efferent arc by the nerves innervating the different muscles of respiration. In addition, afferent impulses may be received by way of the olfactory and optic nerves, because this reflex is also evoked by intense odors and sudden high intensities of light.

(c) Center for coughing. It is situated above the center for respiration. The sensory side of this reflex circuit is formed by the afferent fibers of the vagus, and the efferent arc by the nerves innervating the muscles of the larynx and the expiratory muscles of the thorax.

(d) Center for mastication and sucking. The sensory path includes the second and third branches of the trigeminal and the glossopharyngeus. The motor path includes the facialis to the muscles of the lips, the hypoglossus to the tongue, and the third branch of the trigeminal to the muscles raising and lowering the lower jaw.

(e) Center for deglutition. It is situated near the floor of the fourth ventricle above the respiratory center. The afferent side of this circuit is formed by the second and third branches of the trigeminal and the vagus. Its efferent side is formed by the vagus.

(f) Center for the secretion of saliva. It is placed near the floor of the fourth ventricle and may be activated by different sensory impulses. Its efferent fibers enter the parasympathetic system and appear peripherally as the chorda tympani and the auriculotemporal branch of the inferior maxillary division of the trigeminal.

(g) Center for vomiting. Besides the afferent fibers of the vagus, these impulses may also be derived from other sensory tracts, such as the optic and olfactory. The chief efferent fibers are contained in the vagus.

The Medulla as an Automatic Center.—The foregoing discussion shows that the reflex centers of the medulla are practically identical with the nuclei of the different cranial nerves concerned in these reactions. For this reason, the latter may be considered as generating a state of nervous activity very similar to that displayed by the spinal nuclei or by the cells of the automatic centers regulating the most vital processes in our body, namely, respiration, the action of the heart, and the distribution of the blood. These functions are of such great importance that the medulla is capable of assuming through them a position almost independent of the cerebrum and

allied structures. Inasmuch as it is thus placed in a position to influence the respiratory, cardiac and vasomotor activities, it must also dominate in an indirect way, the function of the cerebral centers.

Lastly, the medulla must be considered as an organ of conduction, because it occupies a position directly in the path of the cerebro-spinal tracts. It also gives origin to several of the cranial nerves which in this way are enabled to gain access to the higher centers. All in all, therefore, the medulla is one of the most widely connected structures of the nervous system.

FIG. 317.—DIAGRAMMATIC CROSS-SECTION THROUGH THE HUMAN MEDULLA OBLONGATA AT THE LEVEL OF THE VAGUS NERVE, ILLUSTRATING DETAILS OF FUNCTIONAL LOCALIZATION. (Herrick.)

CHAPTER LIII

THE CRANIAL NERVES

The Functional System of the Cranial Nerves.—We have seen above that the spinal nerves enter the cord by a series of roots arranged in strict agreement with segmentalism. The sensory fibers and corresponding gray matter occupy the dorsal realm of this structure, while the motor fibers with their gray matter are situated anteriorly. The cranial nerves show a similar functional arrangement, because the sensory centers are situated dorsally to the motor, but the segmentalism observed in the case of the spinal fibers has here given way to a perfectly definite grouping of the different units. This enables all impulses of like character to become closely associated. In general, therefore, it may be said that the twelve pairs of cranial nerves represent twelve pairs of interlocking systems, regulating one or several independent functions, irrespective of their anatomical location. This fact shows that the grouping of the components of the cranial nerves

is based upon function rather than upon structure, and implies that these components are arranged in accordance with their terminations. Thus, the classification of these nerves should be based upon the

FIG. 318.—VIEW FROM DORSAL ASPECT OF UPPER PART OF THE SPINAL CORD, MEDULLA OBLONGATA, PONS, FOURTH VENTRICLE, MID-BRAIN, THALAMUS, ETC., DISSECTED *in situ*. (*J. Symington.*)

type of organ with which they are united peripherally or upon the type of center in which they arise or terminate.¹ Thus, it happens that a certain cranial nerve may embrace fibers from two different

¹ Herrick, Wood's Reference Handbook of the Med. Sciences, iii, 1914, 321.

sense-organs which then diverge centrally to seek the respective centers for these functions. Again, a certain sense-organ may distribute its ingoing fibers to two different cranial nerves, after which they reunite to attain a common center.

This structural divergency implies that the cranial nerves may be efferent or afferent in their function, as well as mixed. The efferent fibers arise, of course, in cells situated within the domain of the cerebrum, isthmus and medulla, while the cells of the afferent fibers are situated in special ganglia at some distance from these parts. In the latter case, the same arrangement is found to exist as in the spinal ganglia, *i.e.*, the sensory cell sends out an axon which soon divides into two branches, one of them tending toward the brain, and the other toward the peripheral sense-organ. The trophic centers of the motor fibers, therefore, are situated within the brain, and those of the sensory fibers in the peripheral ganglia.

With the exception of the first and second pairs, the cranial nerves arise from the medulla oblongata and neighboring parts, their nuclei being situated chiefly in the gray matter below the floor of the fourth ventricle and its prolongation below the aqueduct.

1. The **olfactory nerve**, or nerve of smell, forms the connection between the olfactory region of the nose and the olfactory center. These

FIG. 318a.—DIAGRAM OF THE CONNECTIONS OF THE OLFACTORY BULB. (Herrick.)

fibers arise in the olfactory cells of the aforesaid area, whence they attain the primary center within the olfactory bulb by passing through the cribriform plate of the ethmoid bone. The arborizations formed by these fibers in this particular locality, are known as glomeruli and represent synapses between the primary and secondary olfactory neurons. The latter, which begin here, are known as the mitral cells. Their axons continue inward and form the so-called olfactory tract, ending finally in the secondary olfactory nucleus,¹ at the base of the olfactory bulb. The olfactory center is then attained by three paths which are known as the medial, intermediate and lateral olfactory striæ.

¹ Zwaardemaker, *Ergebn. d. Physiol.*, i, 1902; also: Edinger, *Vergl. Anat. des Gehirns*, Leipzig, 1908.

The center itself contains the following subdivisions: (a) The lateral olfactory nucleus which extends backward into the tip of the temporal lobe of the cerebrum as far as the point of contact between the ventrolateral extremities of the hippocampus and hippocampal gyrus, (b) the medial olfactory nucleus into which the medial olfactory striæ are discharged, and (c) the intermediate olfactory nucleus in the anterior perforated substance in which the intermediate olfactory striæ terminate. These nuclei are intimately connected with other cerebral centers and diverse motor paths, thereby enabling the sensory impressions of smell to become associated with other sensations as well as with the different motor mechanisms. This close correlation permits these nuclei to play the part of reflex centers, in which the olfactory impulses are transferred to efferent paths and to the motor end-organs. In man, these olfactory reflex centers are dominated by a psychic or cortical center which, as will be shown later, occupies the hippocampal convolution, especially its distal end, the uncus. Different association paths connect this area with other cortical centers.

2. The **optic nerve**, or nerve of sight, conveys the impulses from the retina to the thalamus, where they are transferred onward to the center for vision in the occipital region of the cerebral cortex. The essential receptive element of the eye is the retina which forms the innermost coat of this sense-organ and contains neurons of the following four types: (a) The rods and cones, (b) the bipolar cells, (c) the ganglion cells, and (d) the horizontally arranged association neurons. The fibers of the optic nerve take their origin from the ganglion cells, but this does not mean that these elements constitute neurons of the first order. In fact, as the real receptors of the retina are the rods and cones, these elements should be regarded as forming the neurons of the first order of the optic path. Their impulses are transmitted across the external molecular layer to neurons of the second order, the cell bodies of which are situated in the internal granular layer. These data tend to show that the ganglion cells of the retina are already neurons of the third order which then leave the eye through the optic papilla to form the optic nerve proper.

Having reached the optic chiasma at the ventral aspect of the cerebrum, these fibers enter into a decussation which carries them either in part or as a whole to the opposite side of the brain. A complete crossing is effected in fishes, amphibians, reptiles and most birds, and a partial one in man, and the mammals, namely, in those animals in which the visual fields overlap and which possess stereoscopic vision. There is, however, no evidence at hand to show that the crossing in the latter is absolutely symmetrical, because the number of fibers remaining on the same side seems to become the greater, the higher the rank of the animal in the scale of the Animal Kingdom. In man, however, the fovea centralis or yellow spot seems to be innervated bilaterally, *i.e.*, the fibers emerging from this area pass to both visual centers. This crossing carries the fibers from the inner halves of the

retinæ to the opposite side and leaves the fibers from their outer halves on the same side. Thus, the right occipital center innervates the right halves of both retinæ, and the left center their left halves. The yellow spot of each eye, on the other hand, is innervated by both centers.¹

Posteriorly to the chiasma, these crossed and uncrossed fibers continue upward and backward in the form of the optic tracts. Having passed the surface of the thalamus, they divide into two groups, one of which terminates in the lateral geniculate body and the other in the roof of the colliculus of the midbrain. In this way, certain reflex centers are established which are concerned with the movements of the

FIG. 319.—DIAGRAM SHOWING THE PROBABLE RELATIONS BETWEEN THE PARTS OF THE RETINA AND THE VISUAL AREA OF THE CORTX. THE BILATERAL REPRESENTATION OF THE FOVEA IS INDICATED BY THE COURSE OF THE DOTTED LINES. (Schäfer.)

eyeballs, the process of accommodation, and other reactions. This is true especially of the colliculus, while the thalamus seems to be set aside rather as a relay station in the path leading to the visual center situated in the occipital cortex of the cerebrum. The latter, therefore, forms a direct dependency of the cortical center and hence, its importance must increase with the development of the center for vision. We find here, therefore, an arrangement very similar to that previously noted in the case of the olfactory mechanism, *i.e.*, the light impressions received by the retinæ, may actually reach the center for vision to be associated or may be transferred unto a motor path in the lower reflex center situated in the superior colliculus. In the former case, they must first give rise to a psychic impression, and, in the latter, to a simple

¹ Wilbrand and Säger, *Die Neurologie des Auges*, Wiesbaden, 1904.

reflex reaction. This lower center is intimately connected with the path for tactile and auditory sensations by way of the neighboring cerebral peduncle and is closely associated with the nuclei of the third and fourth cranial nerves. Connection is also made here with the other cranial and spinal nerves by way of the fasciculus longitudinalis medialis.

3. The **oculomotor nerve** arises from the oculomotor nucleus situated in the central gray matter near the floor of the aqueduct of

FIG. 320.—DIAGRAM OF THE PRINCIPAL COMPONENTS OF THE OPTIC APPARATUS.
(Cunningham.)

Sylvius. The latter is composed of three groups of cells, namely, (a) a lateral colony of large ganglion cells situated next to the median line below the aqueduct, (b) a smaller median colony consisting of large cells, and (c) a median colony composed of much smaller cells. This nerve is motor in its function and embraces fibers for:

(a) The internal rectus, superior rectus, inferior rectus and inferior oblique muscles of the eye. According to Bernsheimer,¹ these fibers arise in the group of cells constituting the lateral subnucleus. The coördination of these muscles with those of the opposite eyeball, is not under the guidance of the will. This nerve also innervates the musc. levator palpebræ superioris.

¹ Handbuch der Augenheilkunde, Leipzig, 1900.

(b) The sphincter muscle of the iris. These fibers take their origin in the median colony of small cells and terminate in the ciliary ganglion. Here they make connection with postganglionic fibers formed by sympathetic neurons (*nervi ciliares breves*).

(c) The ciliary muscle. These fibers arise in the median colony of large cells and end in the ciliary ganglion. Their postganglionic continuations are formed by sympathetic neurons (*nervi ciliares breves*).

We shall see later that the contraction of the ciliary muscle allows the lens of the eye to become more convex, a condition necessary for near vision. This change is usually accompanied by a constriction of the pupil. These two reactions occur simultaneously and constitute accommodation reflexes. In addition, the pupil is also constricted whenever a high intensity of light is permitted to strike the eye. This

FIG. 321.—NUCLEI OF ORIGIN OF THE THIRD AND FOURTH NERVES.—(From Poirier and Charpy.)

reflex constitutes the so-called light reflex. In accordance with the preceding discussion, it must now be evident that the afferent arc of the circuit for the *light reflex* is formed by the optic tract, and the efferent arc by the oculomotor nerve. Its center lies in the reflex area of the optic tract, *i.e.*, in the colliculus and corpora quadrigemina near the aqueduct of Sylvius. The constriction of the pupil associated with near vision and constituting the so-called *accommodation reflex*, finds its origin in certain sensory stimuli which are set up in the eye muscles whenever the eyes are converged for a near point. The afferent arc of this reflex circuit, therefore, does not encroach upon the optic tract and is not directly concerned with vision.

4. The **trochlear nerve** arises in the trochlear nucleus which is situated in the central gray matter below the floor of the aqueduct just posteriorly to the lateral subnucleus of the oculomotor nerve. These fibers pass horizontally backward and emerge behind the posterior corpora quadrigemina, where they cross in the anterior medullary velum. It is a motor nerve supplying fibers to the superior oblique muscle of the eyeball. The action which this muscle gives rise to, simultaneously with the muscle attached to the opposite eyeball, is not under the control of the will.

5. The **trigeminal nerve** originates from two roots, a small anterior or portio minor, and a large posterior or portio major. The former is motor and the latter sensory in its function. Its motor root arises in part from a small nucleus in the pons and partly from ganglion

FIG. 322.—NUCLEI OF ORIGIN OF THE FIFTH CRANIAL NERVE. (From Poirier and Charpy, after Van Gehuchten.)

cells situated in the region of the corpora, laterally to the aqueduct of Sylvius. Its musculomotor fibers are distributed peripherally through the ramus masticatorius to the different muscles of mastication, as well as to the muscles of deglutition, inclusive of the musc. mylohyoideus, the tensor veli palatini and musc. azygos uvulæ. It also contains secretomotor fibers for the lacrimal gland and sweat-glands, and vasomotor fibers for the tongue and face. The latter, of course, are of sympathetic origin and use the path of this nerve merely as a highway to reach distal parts.

This nerve is of importance chiefly on account of its sensory power, because it conveys the sensations of touch, pain and temperature from the skin of the face, the adjoining region of the scalp, the mucous membrane lining the nasal and oral cavities, and from the teeth and

eyes. Stimuli brought to bear upon its distant receptors, give rise to a large array of reflex actions, such as inhibition of the respiratory movements, closure of the glottis, slowing of the heart-beat, and secretion of the tears and saliva. The trigeminus is also said to convey the sensations of taste from the anterior third of the tongue, but it is more than probable that the taste fibers contained in this nerve, have been derived from the glossopharyngeus or *nervus intermedius*. The sensory fibers of this nerve arise in the Gasserian ganglion in a manner similar to the fibers of the spinal ganglion. Their peripheral branches pass to the sense-organs, while their central branches divide and are arranged as two roots which end (*a*) in the sensory nucleus situated laterally to the motor nucleus and (*b*) in a long nucleus which extends through the entire dorsal portion of the medulla. This arrangement enables the impulses to be relayed from the sensory nucleus of this nerve through the median raphe to the cortex of the cerebrum. In addition, collaterals are sent to all the nuclei of the cranial nerves arising in the medulla, with the exception of the nucleus abducens. It should also be mentioned that this nerve communicates with the ganglion sphenopalatinum and ganglion submaxillare which form the outposts of the sympathetic system of this region.

6. The **abducens nerve** originates in a nucleus situated below the colliculus facialis, and emerges from the posterior edge of the pons. It is a motor nerve and innervates the external rectus muscle of the eyeball. Like the third and fourth cranial nerves, it is under the control of the will, but not when made to act synchronously with others to produce those movements of the eyeballs which are necessary in binocular vision and accommodation.

7. The **facial nerve** arises from a conspicuous nucleus in the tegmental region of the pons and leaves the brain at the inferior margin of this structure, somewhat lateral to the point of emergence of the sixth nerve. It is chiefly a motor nerve and supplies the muscles of the face, those of a part of the scalp, and those of the ear, inclusive of its intrinsic muscles. As such it governs the expression of the face. This may be gathered from the fact that its division is soon followed by a distortion and a drawing over of the paralyzed side of the face toward the normal. This deviation which eventually may also involve some of the bones, is produced by the tonic pull exerted by the muscles of the normal side. In many cases, however, the paralyzed muscles finally show a condition of contracture which then tends to antagonize this pull so that the face again assumes a more normal appearance. Another muscle which takes part in this paralysis is the orbicularis. The inability to close the space between the eyelids exposes the cornea to mechanical and thermal influences which in turn give rise to a copious secretion of lacrimal fluid, and possibly also to inflammatory processes. The paralysis of Horner's muscle prevents the outflow of the tears into the nasal cavity. In view of the fact that the facial nerve also innervates the muscles which have to do

with nasal respiration, its division leads to a loss of movement of the nostrils. Phonation is impaired.

This nerve also contains secretomotor and vasomotor fibers for the submaxillary and sublingual glands which reach their destination by way of the chorda tympani. It also embraces secretomotor fibers for the lacrimal glands which pass through the ganglion sphenopalatinum and reach the second branch of the trigeminus and subsequently the nervus zygomaticus and nervus lacrimalis. Its sensory fibers convey taste impressions from the front part of the tongue. They form the nervus intermedius and are affixed to the chorda tympani and lingual nerves.

FIG. 323.—THE ORIGIN OF THE SIXTH AND OF THE MOTOR PART OF THE SEVENTH NERVE.

VI., Sixth nerve; VII., seventh nerve; a.VII., ascending part of the root of seventh shown cut across near the floor of the fourth ventricle; g, genu of seventh nerve-root; n.VI., chief nucleus of the sixth nerve; n.VI., accessory nucleus of sixth; n.VII., nucleus of seventh; d.V., descending root of fifth; pyr., pyramid-bundles; VIII.v., vestibular root of eighth nerve. (Schäfer.)

8. The **auditory nerve** consists of two groups of fibers possessing a certain anatomical and functional independency. One of them is concerned with hearing and forms its cochlear branch, and the other with the sense of equilibrium and forms its vestibular branch. In the horse and sheep these fibers are in fact absolutely separated from one another throughout their course.

The auditory nerve enters the bulb in two parts, an external and an internal. The fibers of the former are derived chiefly from the cochlea, and those of the latter from the semicircular canals and the vestibule of the internal ear. The first connect with the spiral ganglion of the cochlea and the latter with the vestibular ganglion of the semicircular canals. These peripheral stations are comparable to the spinal ganglia, because the cells composing them send out processes which soon divide into two branches. One of these connects with the

peripheral receptor, and the other with the central nucleus. If we now follow these fibers in the latter direction, we will find that they pursue a separate course; those contained in the vestibular branch ending in the nuclei of Deiters and Bechterew in the cerebellum, and those belonging to the cochlear division in the ventral and dorsal nuclei of the pons. From these primary relay stations the auditory impulses are conveyed onward to the auditory center in the superior gyrus of the temporal lobe of the cerebrum, but the course pursued by them, has not been fully made out as yet. It seems, however, that the largest number of the fibers arising in the ventral or accessory nucleus acusticus, cross to the opposite side of the cerebrum. They

FIG. 324.—THE COURSE AND CONNECTIONS OF THE FIBERS FORMING THE VESTIBULAR ROOT OF THE AUDITORY NERVE.

r., Restiform body; *V*, descending root of fifth nerve; *p.*, principal nucleus of vestibular root; *d.*, fibers of descending vestibular root; *n.d.*, a cell of the descending vestibular nucleus; *D*, nucleus of Deiters; *B*, nucleus of Bechterew; *n.t.*, nucleus tecti (fastigii) of the cerebellum; *pl.b.*, posterior (dorsal) longitudinal bundle. (*Schäfer*.)

select, however, somewhat different routes. Some of them tend directly across through the corpus trapezoideum, while others reach this structure by passing around the restiform body and through the tegmental region. From here they attain the superior olivary body of the same and opposite sides and subsequently the lateral fillet or lemniscus. Having traversed the colliculus or median geniculate body, they terminate eventually in the psychic area for audition, situated in the superior gyrus of the temporal lobe.

The dorsal nucleus or tuberculum acusticum is connected with this center by secondary sensory neurons which form the medullary or auditory striæ, a band of fibers traceable along the floor of the fourth ventricle. At the median raphé these fibers turn and a large

number of them cross the midline to attain the lateral lemniscus of the opposite side, whence they reach the gray matter of either the inferior colliculus or median geniculate body. These structures are connected with the psychic area for hearing by way of the auditory radiation which passes through the inferior extremity of the internal capsule.

We observe, therefore, that the auditory nerve finally gives rise to a decussation which bears a close resemblance to that effected by the optic nerve, but the degree of crossing has not been determined as yet with certainty. As we shall see later, this fact is very important, because it helps to explain some of the symptoms resulting from unilateral destruction of the center of hearing. In the second place, it

FIG. 325.—THE COURSE AND CONNECTIONS OF THE FIBRES FORMING THE COCHLEAR ROOT OF THE AUDITORY NERVE.

r., Restiform body; *V.*, descending root of the fifth nerve; *tub.ac.*, tuberculum acusticum; *n.acc.*, accessory nucleus; *s.o.*, superior olive; *n.tr.*, nucleus of trapezium; *n.VI*, nucleus of sixth nerve; *VI*, issuing root-fiber of sixth nerve. (Schäfer.)

will be seen that the median geniculate body may serve the purpose of a secondary auditory center and hence, assume a position similar to that of the lateral geniculate body which is really a subordinate center for vision. Thirdly, sufficient experimental evidence is at hand to show that the auditory centers form the starting points of certain motor paths which are used in the reflex actions resulting in consequence of auditory stimuli.

9. The **glossopharyngeus nerve** is motor and sensory in its function. It emerges from the side of the medulla, its motor fibers originating from two nuclei, known as the nucleus ambiguus which forms the ventral area of the vagus nucleus, and the nucleus dorsalis which is situated below the floor of the fourth ventricle. Its sensory fibers are derived from the ganglion superiorem and ganglion petrosum. The peripheral branches of these pass to the receptors and their central

branches in part to the nucleus alæ cinereæ and in part to the nucleus tractus solitarii. Its sensory and motor fibers are thereby brought into close relationship with those of the vagus nerve.

Its musculomotor function is restricted to the muscles of the pharynx (musc. stylopharyngeus) and its secretomotor function to the parotid gland. The latter is reached by way of the ganglion petrosum, nervus tympanicus, nervus petrosus superficialis minor, ganglion oticum and nervus auriculotemporalis. Its sensory fibers are in relation with the mucous membrane of the tongue, pharynx,

FIG. 326.—DIAGRAM SHOWING THE BRAIN CONNECTIONS OF THE VAGUS, GLOSSOPHARYNGEAL, AUDITORY, FACIAL, ABDUCENS, AND TRIGEMINAL NERVES. (After Obersteiner.)

tonsils, tympanic cavity and Eustachian tube. It also conveys the sensations of taste from the posterior third of the tongue and the lateral aspect of the fauces.

10. The **vagus or pneumogastric nerve** arises from the same nuclei as the ninth nerve, and emerges from the side of the medulla posterior to the superficial origin of the preceding. It is a mixed nerve. Its motor fibers are traceable to the nucleus ambiguus and the dorsal or vagus nucleus. Its sensory fibers take their origin in the ganglion jugulare and ganglion nodosum and pass to the nucleus alæ cinereæ and, in small numbers, also to the nucleus tractus solitarii. While the function of this nerve will be considered in detail in connection with

the organs innervated by it, it may be stated at this time that it is primarily concerned with respiration, the action of the heart, and the musculomotor and secretomotor processes of the digestive organs.

(a) *Respiration.* It supplies motor fibers to the muscles of the larynx, trachea and bronchi. The most important nerves to be mentioned in this connection are its superior and inferior laryngeal branches. It also serves as the sensory nerve of the larynx (sup. laryngeus) and the lungs. The latter are directly concerned with the self-regulation of respiration.

(b) *The Heart.* The vagus conveys inhibitor impulses to this organ, and also sensory impulses from this region by way of its "depressor fibers."

FIG. 327.—CROSS-SECTION OF MEDULLA SHOWING NUCLEI OF NERVES X AND XII.
(Cunningham.)

(c) *Digestive Organs.* The vagus innervates the sphincters of the pharynx and the musculature of the esophagus, stomach and intestine. It sends secretomotor fibers to the stomach, intestine, pancreas and possibly also to other abdominal organs. The vasomotor mechanisms of these organs are supplied with fibers from the solar plexus. While the latter in turn communicates with the thoracic sympathetic system through the splanchnic nerves, it is also intimately connected with the vagus system.

11. The **accessory nerve** is formed from several upper roots which take their origin in the medulla, and from a series of lower roots which arise from the anterior gray matter of the spinal cord as low as the fifth to seventh cervical vertebræ. It is a motor nerve and supplies the sternocleidomastoid and trapezius muscles.

12. The **hypoglossal nerve** emerges from the furrow between the anterior pyramid and olivary body of the medulla. Its deep origin is formed by a nucleus situated in the floor of the fourth ventricle. A commissure unites the nuclei in the two halves, and each nucleus receives fibers from the opposite cerebral hemisphere. It is a motor nerve and innervates the muscles of the tongue, inclusive of the *musculus geniohyoideus* and *thyrohyoideus*.

SECTION XVIII

THE CEREBRUM

CHAPTER LIV

THE GENERAL FUNCTION OF THE CEREBRUM

General Arrangement of the Gray Matter.—The investigation of the function of the brain of which the cerebral hemispheres form the largest part, is usually carried on along structural, experimental physiological, and clinical lines. A complete functional picture, however, can only be obtained if the data derived from these sources, are compiled and compared with one another. On the histological side, it is of interest to note that the chief neurons of the cerebral cortex are pyramidal in shape and are directed in such a way that their apices are turned toward the surface and their bases toward the white matter. The three poles of these cells are usually occupied by dendrites, the principal one of which arises from the apex. The axon is derived from a hillock in the middle of the base of the cell-body and pursues a rather straight course into the white matter, giving off collaterals in its course.

While this cell is typical of the cerebral cortex, it does not exhibit the same size and form in all parts of this organ. Throughout the cortex, however, it is united with others to form four or five separate layers which border immediately upon the central core of white matter.

(a) The most superficial layer lies, of course, in contact with the enveloping membranes of the cerebrum, *i.e.*, with the pia mater, and is known as the plexiform or molecular layer. Its thickness amounts to 0.25 mm. Besides the neuroglia cells, it contains chiefly dendrites from the deeper layers and a few small cells, the processes of which are directed parallel to the surface of the cortex. These processes terminate within this layer and do not penetrate the white matter. It is believed, therefore, that their function is chiefly associative for the cells of the cortex.

(b) The layer of pyramidal cells lying directly underneath the former, is characterized by the presence of a large number of cells possessing a pyramidal shape. Campbell¹ arranges them in three layers, this classification being based upon differences in their size. The inner ones are larger than the outer. As has been mentioned above, their apices are directed outward and send their dendrites into the molecular layer. The axon arises from the basal margin of the cell and enters the white matter underneath. The dendrites of the pyramidal cells are rough and

¹ Hist. Studies on the Local. of Cort. Function, Cambridge, 1905.

thorny; in fact, it has been claimed that these projections form actual synaptic connections with neighboring neurons.

(c) The stellate or granular layer contains numerous cells possessing a stellate shape and short irregular axons. It is also known as the middle cell lamina.

(d) The inner fiber lamina contains numerous large and medium-sized cells which are known as the cells of Betz. The latter are not present in all parts of the cerebral cortex, but are most conspicuous in its motor area next to the fissure of Rolando. Their axons pass into the white matter.

(e) The layer of fusiform or polymorphous cells is situated next to the white matter. It is also known as the inner cell lamina and is composed of different types of cells of which the spindle-shaped ones are the most prominent. It also embraces a number of pyramidal cells similar to those found in the outer realm of the more superficial layer, but their tips are directed inward and their bases toward the surface. These are the cells of Martinotti. In addition, this layer contains a cell resembling the second type of Golgi with branching axons. The latter terminate in the neighboring gray matter.

FIG. 328.—POSTCENTRAL CONVOLUTION. GOLGI METHOD.

1; Plexiform layer; 2, small pyramids; 3, medium pyramids; 4, superficial large pyramids; 5, granules; 6, deep large pyramids; 7, deep medium pyramids. (Cajal.)

General Arrangement of the White Matter.—The medullary portion of the cerebrum begins directly below the polymorphous layer. When stained in accordance with Weigert's method which brings out the medullated nerve fibers, the white matter is seen to be arranged in radial striæ, *i.e.*, its fibers expand fan-like from a common center formed by the internal capsule. Some of these radial streamers may be followed to the surface of the cortex and may be seen to give rise here and there to networks of fibers which are placed transversely to the course of the former. A layer of this kind is found directly underneath the surface of the cortex, but it does not extend throughout the brain. It is most conspicuous in the hippocampal region. Another layer is situated between the molecular and pyramidal zones, and still another internally to the granular zone. These layers are known respectively as the outer and inner stripes of Baillarger. A special layer of transverse fibers is found in the visual

area of the occipital lobe where it bisects the granular layer. This is

the line of Gennari, which really corresponds to the outer stripe of Baillarger.

It will be seen, therefore, that the cortex of the cerebrum presents a definite histological structure which, however, does not remain the same in its different regions. Certain minor differences appear here and there, which enable us to tell from which particular area a certain section has been taken. In making this distinction, we should be guided by (a) the thickness of the entire cortex, (b) the relative thickness of its different zones, (c) the type of cells found in each layer, and (d) the character of the radial and transverse striæ of fibers. Thus, it is to be noted that the thickness of the human cortex varies from about 4 mm. in its motor region to about 2 mm. in other parts. In the

FIG. 329.—NEUROGLIA CELLS OF CORTEX CEREBRI. GOLGI METHOD. (*G. Retzius*.)

former area are found the large pyramidal cells of Betz which are characteristic motor elements. In addition it is to be observed that the layer of pyramidal cells is very thick, while the granular layer is thin.

The visual area of the occipital lobe is characterized by a very prominent granular layer which, as has been stated above, is really divided into two by a broad band of transverse fibers. The distinguishing feature of the association areas of the frontal, parietal and occipital lobes is the highly developed outer layer of pyramidal cells.

Classification of the Tracts of the Cerebrum.—The fibers of the cerebral white matter are arranged in three distinct groups, namely:

(a) Those which connect the hemispheres with the outlying structures of the nervous system, *i.e.*, with the thalamus, pons, medulla and spinal cord.

¹ Brodmann, *Vergl. Localisationslehre der Grosshirnrinde*, Leipzig, 1909; also Ramon y Cajal, *Stud. über die Hirnr. des Menschen*, Leipzig, 1906, or Lewandowsky, *Handb. der Neurologie*, Jena, 1910.

(b) Those which unite different parts of the same hemisphere with one another, and

(c) Those which extend from one hemisphere to the other. The first group forms the so-called projection system, the second, the association system and the third, the commissural system. Naturally, each area of the cortex must be equipped with two sets of fibers, one of which conducts away from it and the other toward it. In the case of the projection system, the terms of afferent and efferent may be used

FIG. 330.—SCHEMA OF THE PROJECTION FIBERS OF THE CEREBRUM AND OF THE PEDUNCLES OF THE CEREBELLUM; LATERAL VIEW OF THE INTERNAL CAPSULE.

A, Tract from the frontal gyri to the pons nuclei, and so to the cerebellum (frontal cerebro-cortico-pontal tract); B, the motor (pyramidal) tract; C, the sensory (lemniscus) tract; D, the visual tract; E, the auditory tract; F, the fibers of the superior peduncle of the cerebellum; G, fibers of the middle peduncle uniting with A in the pons; H, fibers of the inferior peduncle of the cerebellum; J, fibers between the auditory nucleus and the inferior colliculus; K, motor (pyramidal) decussation in the bulb; VI, fourth ventricle. The numerals refer to the cranial nerves. (After Starr.)

to distinguish these fibers from one another, but this terminology is not applicable to the association and commissural systems, because these fibers establish communication between different central parts and do not possess a true motor or sensory function. The **projection system** is made up of the following afferent and efferent tracts:

A. Afferent. (a) *Thalamocortical*.—These fibers arise in the gray matter of all parts of the optic thalamus and radiate outward to every area of the cerebral cortex. In accordance with their distribution, they are grouped in the form of a frontal, parietal, occipital and ventral stalk. Those forming the first group, do not invariably pass directly to the frontal lobes, but may end in the caudate and lenticular nuclei. Those destined for the occipital lobes, form the so-called optic

radiation. They emerge from the outer part of the pulvinar and external geniculate body.

(b) *The Fillet System of Fibers*.—This is the tract which enables the impulses from the different sensory paths of the cerebrospinal system to reach the thalamus and subthalamic region.

(c) *The Superior Cerebellar Peduncle*.—This tract connects the central ganglia of the cerebellum with the thalamus and subthalamic region. Some of them may pass directly through and around this structure to reach the region of the fissure of Rolando.

(d) *The Auditory Radiation*.—These fibers extend from the internal geniculate body to the temporal lobe. They traverse the posterior extremity of the internal capsule under the lenticular nucleus.

B. Efferent. (a) *The Pyramidal Tract*.—These fibers arise in the motor area of the cortex and pass through the corona radiata into the internal capsule. Here they are grouped in the genu and anterior two-thirds of the posterior limb. In their downward course they enter the crista and pyramids of the pons and medulla. Most of them cross the midline in the upper part of the spinal cord to enter the crossed pyramidal tract. The others continue onward on the same side where they form the direct pyramidal tract, but cross over gradually in the lower part of the cord.

(b) *The frontopontine fibers* take their origin in the cortex of the frontal lobes and eventually gain the mesial extent of the crista of the crus cerebri. They terminate in the formatio reticularis of the pons or nucleus pontis.

(c) *The temporo-pontine fibers* originate from the two upper temporal convolutions and enter the outer extent of the crista. From here they enter the pons, where they terminate in the nucleus pontis and are brought into relation with the middle peduncles of the cerebellum. This path, therefore, serves as the chief efferent bridge between the cerebrum and cerebellum, the afferent connection between these organs being represented by the fibers passing between the cerebellar cortex and dentate nucleus to the superior cerebellar peduncle, red nucleus, optic thalamus and the cerebral cortex of the opposite side.

The association system unites the different areas of the cerebral cortex of the same side with one another. Some of these fibers merely dip downward into the white matter to clear the bottom of the sulci and to enter the cortex immediately adjoining, while others pass to more remote regions. For this reason, these fibers are said to form short and long association paths, the most prominent of which are the:

(a) *Uncinate fasciculus* which connects the orbital convolutions of the frontal lobe with the anterior segment of the temporal lobe.

(b) *Cingulum* which passes between the anterior perforated space and the hippocampal gyrus and temporal lobe.

(c) *Longitudinal superior fasciculus* which forms the connection between the frontal, parietal and occipital cortex.

(d) *Longitudinal inferior fasciculus* which extends along the occipital and temporal lobes.

(e) *Occipitofrontal fasciculus* which is situated internally to the corona radiata and next to the caudate nucleus.

The commissural system consists of three chief bridges which unite the two hemispheres, namely:

(a) *The corpus callosum* consists of fibers which arise in all parts of the cortex with the exception of the anterior and posterior segments of the temporal lobes and the olfactory bulb. They originate in cells of the cortex but may also be the collaterals of certain projection axons. Having reached the other side, they arborize extensively.

(b) The *anterior commissure* connects the olfactory and certain portions of the temporal lobes. It pursues a course through the anterior wall of the third ventricle anterior to the pillars of the fornix.

FIG. 331.—LATERAL VIEW OF A HUMAN HEMISPHERE, SHOWING THE BUNDLES OF ASSOCIATION FIBERS.

A, A, Between adjacent gyri; B, between frontal and occipital areas; C, between frontal and temporal areas, cingulum; D, between frontal and temporal areas, fasciculus uncinate; E, between occipital and temporal areas, fasciculus longitudinalis inferior; C.N, caudate nucleus; O.T, thalamus. (After Starr.)

FIG. 332.—DIAGRAM OF ASSOCIATION, COMMISSURAL, AND PROJECTION FIBERS OF BRAIN.

A, Corpus callosum; B, anterior commissure; C, basal ganglia; D, endings of commissural fibers; E, sensory cortex; M, motor cortex; F, endings of association fibers from motor cortex (collaterals of projection-fibers); G, ending of association-fibers from sensory center; H, projection-fibers from motor cortex passing to spinal centers; I, projection-fibers from sensory cortex; a, b, c, collaterals. (Adapted from Cajal.)

(c) The *hippocampal commissure* is formed in the hippocampus of one side and ends almost wholly in the same structure of the opposite side. It is closely concerned with the sense of smell.

Mode of Development of the Cerebrum.—In early embryonic life the nervous system first presents itself as a dorsal tube, known as

the neural tube. It is formed by an invagination of the epiblast.¹ Its cavity possesses a somewhat larger caliber in front than in the region of the spinal cord, and becomes subdivided into three vesicles by two constrictions. These are designated respectively as the fore-brain, midbrain and hindbrain. To begin with, the walls of this tube are thin, being composed solely of epithelial cells. The nervous elements develop a little later and show a differentiation into neuroblasts and spongioblasts, the former eventually giving rise to nerve-cells and the latter to the supporting tissue or neuroglia. In several places, however, the original epithelium remains undifferentiated and

FIG. 333.—AN ENLARGED MODEL OF THE BRAIN OF A HUMAN EMBRYO 3.2 MM. LONG (ABOUT TWO WEEKS OLD). THE OUTER SURFACE IS SHOWN AT THE LEFT, AND ON THE RIGHT THE INNER SURFACE AFTER DIVISION OF THE MODEL IN THE MEDIAN PLANE. THE ANTERIOR NEUROPORE MARKS A POINT WHERE THE NEURAL TUBE IS STILL OPEN TO THE SURFACE OF THE BODY. THE PALLIUM IS THE REGION FROM WHICH THE CEREBRAL CORTEX WILL DEVELOP. THE OPTIC RECESS MARKS THE PORTION OF THE LATERAL WALL OF THE DIENTECPHALON FROM WHICH THE HOLLOW OPTIC VESICLE HAS EVAGINATED. (After His, from Prentiss' *Embryology*.)

finally gives rise to a layer of similar cells, known as the ependyma. This relationship is shown best in the hindbrain, where the posterior wall of the neural canal fails to develop nervous elements and reaches maturity merely as a layer of epithelial cells covering an expanse of the tube. This is the fourth ventricle. In other places, again, the nervous elements grow very rapidly and lead to the formation of more or less circumscribed structures. The cerebellum, for example, is developed by an offshoot from the dorsal wall of the tube, while the pons and medulla are formed by a more even outgrowth round the entire central canal. The details of the development of the brain lie, of course, outside the scope of this book and must be obtained from works of more specialized character.

¹ Keibel and Mall, *Manual of Human Embryology*, Philadelphia, 1912.

Comparative Physiology of the Cerebrum.—In the course of vertebrate evolution, the primitive reflex stem of the nervous system eventually acquires a number of structures which collectively make up the brain. Its constituent elements are the hindbrain (rhombencephalon), midbrain (mesencephalon), tweenbrain (diencephalon) and forebrain (prosencephalon). The one named last is formed by the cerebral hemispheres. Obviously, these complex masses find their origin in the adjuncts to the head ganglia of the lowest forms which, as has previously been pointed out, are primarily concerned with the formation of the sense of smell, sight, touch, etc. The point to be emphasized is that these areas are developed from small beginnings and that

FIG. 334.—DIAGRAMMATIC REPRESENTATION OF THE HEAD OF A TURTLE, TO SHOW THE POSITION OF THE CEREBRUM *C* AND OPTIC LOBES *O*.

FIG. 335.—DIAGRAMMATIC REPRESENTATION OF THE BRAIN OF A FROG (*A*) AND SHARK (*B*).

ON, Olfactory nerves; *OL*, olfactory lobe; *C*, cerebrum; *T*, tween brain; *Op.L*, optic lobes; *Ce*, cerebellum; *M*, medulla; *Co*, spinal cord; *OC*, olfactory capsules; *OB*, olfactory bulb. The cranial nerves are indicated by Roman numerals.

their mass and complexity is in accord with the position of the animal in the scale of the Animal Kingdom.

Thus, we find that the olfactory realm occupies almost the entire cerebrum of the fishes, and forms the most conspicuous part of the brain of the reptilia and amphibia. This condition permits of only one conclusion, namely, that the sense of smell is especially well developed in these animals, and that their existence is mainly dependent upon olfaction. Moreover, while their reactions are almost wholly reflex, they must also possess a moderate power of associating these sensations. As we ascend the scale of the Animal Kingdom, this sense becomes retrogressive. A constantly increasing number of other mechanisms are added to the hemispheres which enable the animal

to assume a more diversified position in nature. This is true particularly of birds, their more elaborate powers being directly attributable to a greater development of the corpus striatum and cerebellum. In mammals, on the other hand, these bodies remain relatively small, whereas the external shell of the cerebrum, or pallium, is brought into much greater prominence. These differences have led to the division of the constituents of the cerebrum into two groups, namely, those which are intimately associated with the sense of smell, and those which are chiefly concerned with vision, hearing and touch. The

FIG. 336.—MEDIAN SECTION OF AN ADULT BRAIN. (*J. Symington.*)

former are spoken of collectively as the archipallium, and the latter as the neopallium. The first system is the more primitive. Its importance gradually diminishes in favor of the second.

As a natural consequence of this evolution we find that the cerebral hemispheres increase in volume and complexity until, in the mammals, they become larger than the whole of the rest of the brain put together. They overshadow the primitive olfactory apparatus completely, and extend backward across the brain-stem as far as the middle of the cerebellum. In this way, it comes to pass that the primitive reflex cerebrum of the lower forms which is largely apportioned to smell,

is finally changed into the complex association organ of the higher animals. As such it is destined eventually to dominate all processes of life, because it gives rise to the psychic products involved in consciousness, perception, volition, thought and memory. In the higher forms, therefore, all reactions are referable in last analysis to the psychic processes, because while they may not always be the direct outcome of cerebral activity, the latter unfailingly determines the condition of the body as a whole and hence, also the power of reaction of its constituent tissues and organs.

The brain of the higher animals, therefore, possesses a distinguishing feature in its many areas of nervous tissue which are primarily intended to be adjuncts to the different motor and sensory mechanisms. This statement, however, should not imply that they are all psychic in their function; in fact, they are not so to begin with. These additions, as has been stated, bring about an increase in the mass and weight of the brain. Thus, we find that the human brain weighs about 1400 grams in the male and 1240 grams in the female, and is heavier than that of any of the lower forms, excepting the whale and elephant. Even a casual study of the behavior of these three types of animals will show that man is distinctly superior to the other two, and even to those animals which, relatively speaking, possess the same amount of brain tissue.

The reason for this is not difficult to detect. It lies in the fact that a large part of the human brain is taken up by nervous material which gives rise to those associations which are necessary for reflection, intelligence, and volition. In other words, the human brain possesses the distinguishing feature of being more of a psychic mechanism than that of any other animal. It will be seen, therefore, that while the absolute amount of brain tissue of such animals as the dog, ape and man remains practically the same in all three, the human brain has lost much of that kind of nervous material which is ordinarily set aside for motor action and sensation. Instead, it has acquired certain units for the formation of those associations which add a distinct psychic quality to these fundamental processes. This gradual evolution of the cerebral hemispheres, therefore, accomplishes a shifting of function from lower centers to a higher psychic realm situated in the cortex. In the human brain, this transfer of function is portrayed best by the relationship existing between the cortical or psychic centers for vision and hearing and the corresponding lower "reflex" centers situated in the thalamus and geniculate body. In other words, man's position in the scale of the Animal Kingdom is determined by the gradual subordination of these lower centers of the brain-stem to the more recently formed cerebral hemispheres and especially to their cortical portions.

This functional metamorphosis displays itself in an increase in the complexity of the brain rather than in an increase in its weight. Thus, we find that the rabbit's brain presents a very smooth surface,

while that of the cat, dog and ape is decidedly uneven, *i.e.*, it is crossed by furrow-like depressions or sulci which divide it into numerous convolutions and lobes. Its greatest complexity it attains in man, but even here certain differences are apparent in that the brain of the more primitive

FIG. 337.—LEFT CEREBRAL HEMISPHERE FROM THE LATERAL ASPECT. (*J. Symington.*)

FIG. 338.—LEFT CEREBRAL HEMISPHERE FROM THE MESIAL ASPECT.

The label "caput hippocampi" has been placed too far forward. The caput hippocampi does not extend in front of the incisura temporalis. (*J. Symington.*)

races is poorer in convolutions than that of the more advanced peoples. In addition to these external differences, we are also able to make out certain internal peculiarities which pertain chiefly to the structure of the

cortex. In the rabbit, for example, the polymorphous layer displays a thickness three times greater than that of the pyramidal layer, whereas in man just the reverse relationship exists. The inference to be drawn from this is that the pyramidal cells are the association units of the brain, excepting, of course, the cells of Betz which are motor in their function, while the polymorphous elements are concerned with the lower types of function. By exclusion, we may then assign a sensory function to the constituents of the granular layer.

This analysis should also take into account that the "psychic" brain of man exhibits certain minor differences in regard to the relative size and complexity of its different association areas. One or the other of these may be more highly developed with the result that the mechanism of which the area so favored forms a part, possesses a greater functional adaptability. In other words, it frequently happens that these association centers are not evenly balanced. It need scarcely be emphasized that such differences may also be displayed by one and the same association area belonging to the brains of different individuals, *i.e.*, one or the other person may excel in certain motor or sensory actions.

Removal of the Cerebrum.—The preceding discussion may well be amplified by a study of the behavior of animals which have suffered a partial or complete loss of the cerebral hemispheres by disease or surgical operation. While the symptoms appearing subsequent to the latter procedure vary somewhat in different animals, they present nevertheless the same general characteristics. The essence of these changes is that an animal, the cerebrum of which has been removed, is devoid of associations. Its psychic life, whether simple or complex, has been destroyed. It has been converted into a simple reflex machine. This fact will be brought out more clearly by a brief consideration of the functional capabilities of decerebrated fish, amphibia and reptilia. These animals are selected for this purpose partly because their cerebrum is sufficiently compact and easy of access to permit of its quick removal, and partly because the positive results following this operation are so few that they do not overshadow the principal effect briefly alluded to above. As this operation is performed under ether, these animals should, of course, be permitted to fully recover before they are studied.

Emphasis should be placed upon the fact that the loss of the cerebrum destroys the sensorium. The decerebrated bony fish (shark)¹ shows the same power and manner of movement as a perfectly normal animal. It tends, however, to be more inactive, assuming a rather continuous position of rest which is changed to one of activity only upon stimulation. But when made to move, its motor reactions show no deviation from normal. More decided defects, however, appear when the lesion is extended to the midbrain, because the animal then is rendered blind and loses its sense of equilibrium.

¹ Bandelot, *Ann. d. sc. nat.*, 105, 1864.

Quite similarly, a decerebrated frog¹ shows few modifications in its behavior, excepting those directly referable to the loss of the sense of smell. It retains a normal posture and jumps and swims normally. It rights itself when placed upon its back, and executes centrifugal and balancing motions when placed upon a rotating disc. Provided that the thalamus has not been injured, it avoids obstacles placed in its way, and reacts to stimuli applied to the nasal mucous membrane by various protective movements. These reactions, however, it shows only when stimulated. Its normal attitude is one of inactivity, because it has lost the memory of past experiences and instincts. For this reason, it need not surprise us that an animal of this kind takes no food but must be fed; in fact, the food must be placed directly into its mouth. The processes of deglutition and digestion are in no way impaired, and hence, it is possible to keep this animal for many months or even for years. A general idea regarding the function of the cerebrum may be had from the character of the croaking reflex before and after the removal of the hemispheres. Under normal conditions, this act is a complex association phenomenon; *i.e.*, this sound is produced only in consequence of definite cortical processes, and is under the guidance of the will. In the absence of the cerebrum, on the other hand, it is a pure reflex, so that it may be elicited at any time by the proper kind of stimulation consisting in a gentle pressure upon the lateral aspects of the chest and abdomen. Furthermore, if we pass our hand over a number of normal frogs, these animals will immediately make motor efforts to escape from the area of stimulation, while the decerebrated animals will not. In brief, we may say that the latter have lost their associations and are no longer under the control of motives or sensations of fear.

The same general effects are manifested by birds² when deprived of their cerebral hemispheres. They assume a position of rest, generally upon one leg with the head drawn in and the bill buried in the feathers. Every now and then they will open their eyes, stretch themselves, and walk about in the cage. This nonresponsive attitude may be disturbed at any time by stimulation, *i.e.*, the animal may be made to fly by throwing it some distance into the air, or it may be made to execute balancing movements upon a rope swung back and forth. It will right itself immediately if placed upon its back, and continues to move about if made to do so. In all these cases, however, the position of rest is sought very soon after the stimulation ceases. Its reactions are machine-like, and are executed without definite purpose or regard to environment. This is well shown by the decerebrated pigeon which, when made to fly, soon alights upon any object situated in its path even if it should endanger its life. As all its digestive processes and spinal reflexes are perfectly normal, this pigeon may be kept for an indefinite period of time provided, of course, that it is

¹ Blaschko, Sehzentrum der Frösche, Berlin, 1880.

² Bechterew, Archiv für Physiol., 1890, 489.

fed and properly attended to. In fact, its initial lethargy is partially compensated for in time, owing to the gradual development in the lower centers of certain activities previously suppressed.

The removal of the cerebral cortex in mammals presents several technical difficulties and is attended by certain motor and sensory defects which do not permit of a precise analysis. Still, it is easily noted that this operation does not destroy the ordinary spinal and basal reflexes and does not lead to a complete disarrangement of the motor functions. This is true not only of rabbits, guinea pigs, and cats,¹ but also of dogs. Directly after the operation, these animals showed a spastic rigidity of their extremities, the so-called decerebrate rigidity,² as well as an extensor tonus and an upward deviation of the head, or opisthotonos. These symptoms disappeared in the course of a few days, whereupon the animal was capable of making relatively precise muscular movements.

The dogs of Goltz³ were operated on at intervals of several months, a part of the cerebrum being removed each time. They were kept for 51 and 92 days and one for 18 months. On autopsy it was found that they had retained small portions of the striate body, optic thalamus and uncus. All these parts, however, were soft and atrophic and in all probability functionally useless. The animals began to move about within a few days after the operation and even walked across inclined planes. They rested by assuming the usual position, but could not be kept in a normal nutritive condition, in spite of the fact that they were rather overfed. They reacted to sensory stimuli by snarling, barking and the erection of the ears, but not in a way to display recognition or to effect an intelligent motor response. Their spinal reflexes remained normal. The animal which was kept longest, finally acquired the power of taking food without being helped, although it had to be held directly under its nose. Food with a disagreeable taste was not swallowed. In general, therefore, these animals displayed the same defects as the birds, reptilia and amphibia, namely, a loss of understanding and memory which made willful and purposeful motor responses impossible. Only the simple reflexes were retained, namely, reactions which do not involve complex associations. The condition of these animals was one of general imbecility.

It has previously been emphasized that the development of the cerebral hemispheres in the higher animals leads to the gradual transfer of at least a part of the motor processes to this realm. This implies that they are finally subjugated to the activities of the cortex. As this higher control must, of course, be most complete in the apes and man, it may be inferred that the destruction of parts of their cerebrum must give rise to symptoms which are much more intense and lasting than those previously noted in the case of birds, reptilia and

¹ Probst, *Jahrb. für Psych. und Neurologie*, 1904.

² Sherrington, *Phil. Transactions*, London, 1896.

³ Pflüger's *Archiv*, iii, 1892, 570.

amphibia. It appears, however, that the general deductions then made, also hold true in the case of man. We know this from a study of the behavior of infants born with cerebral defects as well as from a study of the symptoms following accidental injuries to the cerebral cortex. The cases of inherited absence of the cerebrum or anencephalus, recorded by Vaschide and Vurpas¹ as well as by Sternberg and Latzko,² have shown that the spinal reflexes are preserved and that muscular movements are possible, and especially those concerned with mastication, sucking, crying and grasping. The anencephalous infant described more recently by Edinger and Fischer,³ lived for nearly four years. At autopsy it was shown that its cerebral hemispheres had been displaced by fluid, creating a condition similar to hydrocephalus. During this time it showed no signs of intelligence, but its motor defects were so slight that even its mother did not believe that anything was wrong with it until, when about two and a half years old, it began to show extensive contractures and absolute lethargy.

The destruction of considerable portions of the brain does not prove fatal as a rule unless the injury extends beyond the cortex of the anterior and central convolutions. In fact, the superficial region of one whole hemisphere may be rendered functionally useless without terminating the life of the individual. A process of gradual exclusion of the cerebral cortex is at work in advanced stages of insanity, when the psychic life is terminated more and more until the human body is finally reduced to a machine-like reflex existence, effected with the help of the more deeply seated subsidiary centers.

CHAPTER LV

CEREBRAL LOCALIZATION

THE MOTOR AREA

The Functional Separation of the Cerebral Cortex.—The doctrine that consciousness in its various aspects is the product of several individualized functions of the brain, was first developed by Galenus (131–203 A.D.), although the cerebral hemispheres have really been regarded as the material basis of consciousness since the time of Hippocrates (460–377 B.C.). In fact, it is claimed that this view was first expressed by Alkmeon of Croton in about the year 500 B.C. The imaginative qualities were said to be seated in the frontal, intelligence in the central, and memory in the posterior regions of the cerebrum. This conception that consciousness is composed of separate units and

¹ *Compt. rend. de l'acad.*, cxxxi, 1901.

² *Deutsche Zeitschr. für Nervenheilk.*, xxiv, 1903, 209.

³ *Pflüger's Archiv*, clii, 1913, 535.

that, therefore, the cerebral cortex is divisible into several minor organs, has been made use of by Gall,¹ a physician of Vienna, in framing his system of cranioscopy, or, as it was called later on by Spurzheim, the science of phrenology. Being of the firm belief that the psychical power of an individual is seated in the cerebrum, he outlined definite areas upon the external surface of the cortex in accordance with definite mental qualities. This localization he based upon a study of the external characteristics of the cranium of people who showed especially well-marked mental faculties. He reasoned that the cerebral area controlling a certain function must increase in volume in proportion to the state of development of the latter; moreover, this internal change must betray itself in a greater prominence of the skull plate of this particular area. While this deduction is in general correct, Gall carried it too far, and was in no position to furnish experimental proof for his assertions. These facts were subsequently exploited for commercial purposes and no definite scientific good was derived from them, at least, not immediately.

This assumption of Gall that the cerebrum is not a single organ or functional unit, was first criticised by Flourens,² and his followers Magendie, Longet, Budge and Schiff. It was finally pointed out that the mental life of man cannot be subdivided into a series of independent faculties, this conclusion being based upon the theoretical and experimental data of different writers. Thus, Flourens showed that the destruction of the cerebrum of pigeons is followed by a loss of intelligence which it is impossible to grade by a partial destruction of this organ. In other words, the successive removal of certain parts of the cerebrum did not give rise to a progressive series of psychic defects, but to a uniform lowering of the sum total of the psychic processes. This inability to localize certain functions in definite areas of the cortex led him to believe that the cerebral hemispheres act as a uniform whole and produce the phenomena of consciousness jointly. This conclusion found substantiation in the symptoms displayed by individuals who had suffered accidental injuries of the brain. It will be shown later on that this conception of Flourens is correct only in part, because subsequent researches have proved beyond doubt that there is a distinct difference in the functions of the different parts of the cerebrum, or rather in the quality of the contribution which they severally make to consciousness. Flourens, however, was correct in his belief that the psychic life is really dependent upon a proper functional interaction of the different constituents of the brain.

This doctrine of Flourens was commonly accepted until Broca (1861) gave final proof of the fact that the loss of speech so frequently associated with apoplexy, is due to the destruction of the left inferior

¹ *Recherches sur la syst. nerv. en general et sur celui du cerveau en particulier*, 1810.

² *Recherches expérimentales sur les propriétés et les fonctions du syst. nerv. dans les animaux vertébrés*, 1824.

frontal convolution. This conclusion was based in part upon the earlier work of Bouillaud (1825) which tends to show that the speech center is situated in the anterior extremities of the frontal lobes. Furthermore, it was proved by M. Dax and G. Dax (1836) that in right-handed people this area is confined to the left cerebral hemisphere. Attention has also been called repeatedly to the observation of Galenus that a paralysis of the body results in consequence of lesions to the cerebral hemisphere of the opposite side. These data, however, were not considered of sufficient importance until Broca called special attention to them.

In 1864 H. Jackson, stimulated by the work of Broca, proved that the muscular spasms characterizing epilepsy, are due to an excitation of the cerebral cortex. A firm basis was given to this view in 1870 by Fritsch and Hitzig,¹ who showed that the cortex of the cerebrum is irritable and that its stimulation evokes perfectly definite muscular responses. These tests were first made upon dogs, but were later on extended to other animals and also to the apes and man by Ferrier, Horsley, Schaffer, Sherrington, Luciani, and others. As a direct result of this work, we find a complete abandonment of the doctrine of Flourens and the acceptance of a view which may be said to be more directly in line with the conception of Gall. As has been pointed out above, the latter regarded the cerebrum as a plurality of organs. In its modified form this doctrine holds that the cerebrum is composed of circumscribed areas possessing different sensory and motor functions. Emphasis is placed upon the fact that these parts are not separated from one another, but are intimately associated and inter-related with one another so as to yield coördinated function. This fundamental conception is in no way altered by the doctrine of Flechsig (1894) which asserts in addition that the different areas of the cerebral cortex consist of projection and association fields. In other words, the different cerebral spheres seem to be built up of a central core and a peripheral zone which possesses a true psychic character.

The Location of the Motor Area.—The discovery of Fritsch and Hitzig, that the cortex of the brain is irritable, completely overthrew the old conception of Haller, which assumed that only the underlying white matter is pervious to stimuli. The latter view prevailed for so long a time, because it was advocated by such experimenters as Magendie, Longet, Mateucci, Budge and Schiff, and was based chiefly upon their inability to evoke motor reactions by the stimulation of any area of the cerebral surface. As Fritsch and Hitzig made use of the galvanic current, which tends in time to induce electrotonic alterations, their localization left much to be desired. They showed, however, that the muscular effects are confined to the opposite side of the body and may be varied in their intensity by changing the strength of the

¹ Arch. für Anat. und Physiol., 1870, 300.

current. The finer details were brought out subsequently by Ferrier¹ by means of faradic stimulation.

The motor area is situated along the fissure of Rolando (sulcus cruciatus) of each hemisphere and occupies the anterior and posterior central convolutions. Each area is composed of a number of motor points, so-called, because their stimulation with fine electrodes gives rise to contractions of only one particular muscle or group of muscles. In mapping out this field, it is also to be noted that these motor points are arranged in a definite manner, those governing the activity of the muscles of the trunk being situated very close to the longitudinal fissure, and those controlling the posterior extremity upon the upper-

FIG. 339.—LATERAL VIEW OF THE BRAIN OF A DOG. DIAGRAM INDICATING THE LOCATION OF THE MOTOR AREA.

CS, Crucial sulcus; T, L, A and F, areas for the muscles of the trunk, leg, arm and face.

FIG. 340.—DIAGRAM SHOWING THE MOTOR POINTS IN THE CEREBRUM OF THE DOG.

most convexity of the cerebral surface. Directly below this field we find the motor points for the anterior extremity and at a still lower level those for the facial muscles. In general, therefore, it may be stated that each motor area is composed of four minor fields which control respectively the movements of the trunk, leg, arm, and face. Each minor field is subdivided in turn into still smaller ones, the so-called motor points.

This finer subdivision of the motor areas is not apparent in such mammals as the rabbit, cat, and dog, but becomes unmistakable in the monkeys and reaches its highest development in the apes and man. While only very general reactions can be evoked in rabbits, the cat and dog show movements of a more specialized character. This may be gathered without difficulty from the preceding Fig. 340, illustrating

¹ Les fonctions du cerveau, Paris, 1878.

the position and functional character of the motor points in the dog. It is to be noted especially that they are situated on both sides of the crucial sulcus and are sufficiently centralized to permit, for example, the separate activation of the flexors of the anterior and posterior extremities and other rather specialized movements, such as the retraction and abduction of the fore limbs, movements of the tail, closure of the eyelids, constriction of the pupils, movements of deglutition, and others.

The movements themselves are in no way different from those produced in the course of the normal volitional efforts of the animal.

FIG. 341.—LOCATION OF MOTOR AREAS IN BRAIN OF CHIMPANZEE.

The different motor points lie in front of the fissure of Rolando, partly within the sulci. The area marked "eyes" yields conjugate movements of the eyes, but is generally not taken to be a part of the motor area. (Sherrington and Greenbaum.)

This implies that they are never antagonistic to one another, for the reason that, having evoked a contraction of the flexors, the extensors are momentarily inhibited, and *vice versa*. This preponderance of one set of muscles, even when the stimulation involves the motor points of both groups, may be destroyed by rendering the nervous structures more irritable by means of strychnin or the toxin of tetanus. Under this condition the cerebral stimulation spreads, activating the entire reciprocal mechanism. We then obtain a strife between the antagonistic muscles with the result that the stronger ones predominate.

As has been emphasized above, the effect of the stimulation of the motor area is unilateral, and is restricted to the side opposite the excitation. There is one exception to this rule and that is conjugate movement. Thus, it will be noted that the stimulation, say of the

right motor points controlling the muscles of the eyes, produces a deviation of both eyes toward the left. In this case, therefore, an activation of the right internal and left external recti results which is associated with an inhibition of the right external and left internal recti. The same holds true of other movements which are carried on with the help of corresponding muscles on the two sides of the body, such as the erection and flexion of the trunk, the approximation of the jaws, and the contraction of the muscles of the abdominal wall. Clearly, these movements must be bilaterally controlled and coördinated. A bilateral representation is also had in the case of the respiratory muscles, because, as will be pointed out later, the destruction of one motor area does not affect the respiratory movements.

The observations of Sherrington and Greenbaum¹ have shown that in the anthropoid apes the motor area is confined to the anterior

FIG. 342.—MESIAL SURFACE OF CHIMPANZEE, SHOWING THAT THE MOTOR AREAS ALSO DIP INTO THE LONGITUDINAL FISSURE. (Sherrington and Greenbaum.)

central convolution, but this discovery is not wholly new, because a very similar condition has already been proved by Fritsch and Hitzig to exist in the monkey. These tests have been extended to man by Bartholow and Sciamanna, but particularly by Ferrier (1890), Horsley, Brevior (1890), and Bechterew (1899). The more recent work of F. Krause² in particular tends to prove that the localization in man is very similar to that found in the anthropoid apes. The motor points are concentrated in the precentral convolution and neighboring portions of the frontal furrows and permit of the production of very specialized movements.

The Motor Area is a True Center.—Fritsch and Hitzig characterized the motor area as a center for the production of muscular motion.

¹ Proc. Royal Soc., London, lxxii, 1903.

² Lewandowsky, Die Funktionen des zentralen Nervensystems, Jena, 1907.

This conception is correct, because it has subsequently been shown that the stimulus arises in the gray matter of the cerebral cortex and not in the fibers leading away from this area. This is proved by the fact that the latent period, *i.e.*, the time elapsing between the moment of the application of the stimulus and the beginning of the muscular movement, is longer when the stimulus is applied to the surface of the gray matter than when brought to bear directly upon the underlying white matter. This result clearly betrays the controlling influence of the cells composing this area. Central formative processes always consume a much longer time than the mere passage of the impulses over nerve-tissue. In addition, it has been proved that the gray matter possesses a lower threshold value of stimulation than the white matter. In other words, a lesser strength of current is required for its activation than for that of the underlying fiber substance. This relationship, however, may be reversed by painting the cerebral surface with cocain or chloral.¹

In this connection it should be stated that muscular movements may also be evoked by the stimulation of very restricted areas of the occipital and temporal lobes. These movements, however, remain confined to the extrinsic muscles of the eyes and ears and seem, therefore, to be the direct outcome of the psychic processes occurring in these particular areas. The impulses here generated are transferred first of all to the motor area in the precentral convolution and later on to the distant motor organs. Hence, neither the occipital nor the temporal lobes should be regarded as true motor centers, although both are in a position by means of close association paths to activate the chief motor center in the anterior central region.

Traumatic Epilepsy.—It has previously been stated that the muscular spasms associated with epileptic seizures, have been attributed by Jackson² (1864) to a mechanical irritation of a particular area of the cerebral cortex. This assertion, which was made sometime before the publication of the work of Fritsch and Hitzig, was based upon the fact that certain types of epileptics present definite lesions of the cerebral gray matter. A few years later it found confirmation in the observation of Fritsch and Hitzig proving that the application of a strong galvanic current to the surface of the motor region gives rise to powerful and lasting muscular contractions. Ferrier, Luciani and Unverricht³ showed subsequently that these seizures need not remain localized, but may acquire a progressive character until they involve the musculature of practically the entire body. So generalized, they constitute the clinical picture which is commonly seen during the convulsive seizures of epileptics. It is true, however, that an increase in the strength of the current is not the only means by which these

¹ Francois—Frank and Pitres, *Arch. de Physiol. norm. et. path.*, 1883.

² Hitzig, H. Jackson und die motor. Rindenzentren im Lichte der physiol. Forschung, Berlin, 1901; also: H. Jackson, *A Study of Convulsions*, London, 1870.

³ *Archiv für Psychiatrie*, xiv, 1880, 175.

general seizures may be evoked. In many cases even weak stimuli suffice, provided, of course, that the nervous system has been rendered especially susceptible. Conditions of this kind often arise in the course of eclampsia, uremia, and diabetes, after the toxins contained in the blood have led to a constant discharge of supraminimal impulses. Thus, Landois¹ has succeeded in evoking tonic and clonic spasms by spraying the motor areas with creatin, creatinin and urates. The same results may be obtained with such agents as santonin, physostigmin and bile, and even more readily in pregnant animals,² in which the nervous system is in an especially irritable condition.

Traumatic or Jacksonian epilepsy most commonly finds its origin in tumors or in the pressure exerted upon the motor area by the projecting pieces of bone of an old fracture. These seizures are ushered in as a rule by a feeling of numbness and a tingling sensation in the part to be affected first. Thus, if the motor points of the muscles of the thumb are the seat of the excitation, the contractions begin in this part and then spread to the muscles of the hand, forearm, arm and shoulder, and later on to those of the face, trunk and leg. Eventually they also involve the muscles of the opposite side of the body. This orderly sequence or "march" is also observed if the contractions begin with the muscles of the toes or foot. When these seizures are reproduced in animals, it is quite impossible to prevent the spreading of the contractions from one side of the body to the other by cutting the corpus callosum. Single muscles, however, may be prevented from participating in the general convulsion by ablation of the corresponding motor district. It seems, therefore, that the aforesaid spreading is made possible through the mediation of the subcortical paths and centers.

These seizures may last a few seconds or several minutes. They consist as a rule of a tonic and a clonic phase. To begin with, the muscles remain tonically set, but presently show repeated attempts at relaxation. These relaxations are separated from one another at first by intervals of several seconds, but gradually become more frequent toward the end of the convulsion. In consequence of these violent muscular contractions, the body temperature most generally shows a rise of several degrees, but consciousness is not lost unless the attack is severe. This fact really serves as one of the differential signs between Jacksonian and idiopathic epilepsy. The latter is a type of epilepsy which must be assigned to general retrogressive changes of the cortex. It need scarcely be mentioned that the traumatic type may be remedied by removing its cause, the seat of the lesion being suggested by the manner of progression of the muscular contractions. For example, if the epileptic seizure begins with tonic and clonic spasms of the muscles of the thumb, it is to be inferred that the difficulty chiefly

¹ Wiener med. Presse, 1887.

² Bickel, Pflüger's Archiv, lxxii, 1898, 190, also: Blumenreich and Zuntz, Arch. für Physiol., 1901.

involves the motor points of this particular part. The location of the trephine opening may then be determined with almost mathematical precision.

Effects of the Ablation of the Motor Area.—In dogs, the destruction of one motor area results in an incomplete paralysis of the muscles of the opposite side of the body. This condition is known as hemiplegia, the term biplegia being used when both sides are affected. While this muscular disturbance usually attains its height within a few hours after the injury, it gradually becomes less acute later on and disappears in the course of a few days. During the interim, however, the dog betrays a decided weakness of the muscles situated on the side opposite to the injury, and generally walks upon the back of the paws. Furthermore, those muscles which usually act together, never exhibit so decided a degree of paralysis as those which are not directly related.

FIG. 343.—DIAGRAM ILLUSTRATING THE DISPOSITION OF THE MOTOR AND SENSORY POINTS IN THE BRAIN OF THE DOG (A) AND THE BRAIN OF THE MONKEY (B).

In the former animal motor and sensory paralysis generally occur together, because their points intermingle, while in the apes and man they do not.

Consequently, the muscles of respiration and those of the trunk in general are weakened but never paralyzed. This fact indicates that they are innervated by both hemispheres.

These motor disturbances are associated as a rule with a very decided loss of the tactile sensations and the muscle sense. It appears, therefore, that the motor area of the dog, *i.e.*, the anterior and posterior central convolutions of each side, also embraces certain sensory points, representing the end stations of the incoming fibers pertaining to these sensations (Fig. 343). This intermingling of the motor and sensory points, however, is not in evidence in the monkeys, apes and man. It will be shown later on that in these animals the former are concentrated more and more in the precentral and the latter in the postcentral convolution, inclusive of the neighboring region of the parietal lobe. Hence, it is possible to obtain in these animals a motor paralysis which is not accompanied by disturbances of sensation. Conversely, they may show sensory anesthetics without loss of motion.

In the monkey, the ablation of the motor area gives rise to very marked and permanent symptoms. Very instructive observations have been made by Goltz upon macacus whose left frontal and parietal cortex had been removed by two operations. The animal remained under observation for eleven years. The decided hemiplegia following directly after the operation, gave way in the course of two months to a more moderate paralysis of the muscles of the right side. This disturbance, however, persisted so that the animal always retained a certain clumsiness of movement. It also showed certain sensory defects for the obvious reason that the lesion also involved the post-central and parietal gyri. In walking, climbing and jumping the muscles of the left side were always relied upon most; in fact, unless made to use the right hand, the animal preferred to employ the left hand. It appears, therefore, that the motor area of the monkey is of much greater functional importance than that of the dog for the reason that it is concerned with those higher forms of movements which can only be acquired by training and experience. Obviously, it is more difficult to reestablish a center for skilled movements than it is to compensate for the loss of a center controlling the less specialized movements of the dog. This deduction is in complete harmony with the greater specificity of the pyramidal system of the higher animals as well as with the fact that the motor functions of the latter have gradually been brought under the control of the cerebral hemispheres. This is true especially of man in whom almost all muscular actions are dominated by the cerebrum. It need scarcely be emphasized that this higher innervation necessitates experience and education, two processes which are not essential to the lower forms, because their actions are largely determined by subcortical centers. For this reason we cannot be surprised at the helplessness of infants as against young animals much lower in the scale of the Animal Kingdom.

In further analysis of this subject matter it may be inferred that the recovery from lesions of the motor area must be least complete in man. The histories of such cases show that this injury is invariably followed by a contralateral paralysis, the extent of which is proportionate to the size and severity of the central defect. Moreover, in those cases in which the lesion remains confined to the anterior central convolution, no true sensory disturbance arises.¹ It is also to be observed that the paralysis involves chiefly those muscles which are under the guidance of the will and are not paired in function. In other words, the muscles of respiration, such as the diaphragm, the abdominal and intercostals and those of the larynx, are excepted. While a certain recovery from the immediate effects of the lesion may take place in the course of time, hemiplegic muscles never regain their normal usefulness.

It has been mentioned above that hemiplegia is frequently asso-

¹ Monakow, *Ergebn. der Physiol.*, 1902.

ciated with contractures of the paralyzed muscles, while paraplegia resulting in consequence of the division of the spinal cord or higher conducting paths, is not. This hypertonic setting of the muscles may be explained by the assumption that the injury to the cerebrum has removed those inhibitory impulses which ordinarily tend to hold the tonic discharges of the ganglion cells in check. In consequence of this removal of cerebral inhibition the lower reflexes have full sway and are enabled to play upon these muscles repeatedly until they are thrown into a state of spastic rigidity or contracture. "High" lesions, therefore, increase the spinal reflexes, while "low" lesions tend to diminish them, thereby allowing the muscles to remain continuously in a flaccid condition.

The foregoing discussion should also have made it clear that the motor area constitutes a center for voluntary movements. This statement, however, does not imply that this area, in conjunction with the faculty of volition, is the primary exciting agent of all muscular movements. A conclusion of this kind cannot be correct for the reason that all our actions result in consequence of sensory impressions, and are, therefore, not spontaneous. As the motor area, together with the pyramidal system, forms merely the efferent arc of the association or reaction circuit necessary for motion, it cannot be regarded as a thoroughly independent unit capable of generating centrifugal impulses unaided. The afferent impulses and subsequent sensory impressions ordinarily responsible for the activation of this motor system, are derived from the different association centers of the cerebrum with which we will become acquainted in the chapter now following.

CHAPTER LVI

CEREBRAL LOCALIZATION (CONTINUED)

THE BODY-SENSE AREA

The Location of the Body-sense Area.—While it is undoubtedly true that, in the lower animals, the sensory and motor areas overlap to such an extent that it has been suggested by Bastian to apply to them the more general term of kinesthetic area,¹ the more recent experimental work has shown that, in the apes and man, these fields find a natural boundary in the fissure of Rolando.² Thus, it is now commonly accepted that the motor area lies in front of this sulcus and the sensory area posterior to it. It must be evident, therefore, that a hemiplegia need not be associated with a hemianesthesia, unless

¹ Luciani and Seppilli, *Le Localizzazioni funz. del cervello*, Napoli, 1885.

² Von Monakow, *Ergebn. der. Physiol.*, 1902.

the lesion also involves the posterior Rolandic region. Hence, an injury, involving the entire centro-parietal field, must always be accompanied by a loss of cutaneous sensation.

Monakow does not give a definite boundary for this sensory region, but merely states that it embraces the posterior central gyrus and the

FIG. 344.—HUMAN BRAIN SHOWING OUTER (A) AND MESIAL (B) SURFACES, AND THE SITUATION OF THE CHIEF MOTOR AND SENSORY AREAS.

The different shading represents the extent of each of these areas as determined by a study of the histological structure of the cortex. (Campbell.)

anterior realm of the superior to inferior convolutions of the parietal lobe. Flechsig's view¹ coincides with this localization. He especially emphasizes the fact that the sensory points are centralized in the con-

¹ Sächs. Gesellsch. der Wissenschaften, Leipzig, 1904.

vexity of the posterior central convolution, while the Rolandic sulcus itself is already partly motor. This deduction which is based chiefly upon histological evidence, has been greatly strengthened by Cushing,¹ who, for reasons of diagnosis, resorted to the stimulation of the centroparietal region in two conscious patients. The positive statement is made that distinct sensations of numbness and touch were aroused which persisted as long as the stimulation remained confined to the post-Rolandic area. This evidence is in agreement with the distri-

FIG. 345.—SCHEMA REPRESENTING THE ORIGIN AND COURSE OF THE FIBERS OF THE MEDIAN FILLET—THE INTERCENTRAL PATHS OF THE FIBERS OF BODY SENSE. (Howell.)

bution of the afferent paths of the spinal cord and principally of those fibers which form its posterior funiculi. We know that the impulses arriving in the nuclei of these tracts, are transferred to secondary neurons forming the internal arcuate bundle, which crosses the mid-line in front of the decussation of the motor (pyramidal) tracts. This fact is important, because it explains the contralateral character of defects in these sensations. Beyond their decussation the sensory

¹ Amer. Jour. of Physiol., xxiii, 1909.

fibers form a longitudinal bundle which is designated as the median fillet or lemniscus. They terminate chiefly in the thalamus superior colliculus of the corpora quadrigemina, receiving in their course numerous fibers from the sensory nuclei of the cranial nerves of the opposite side. The thalamus is connected by tertiary neurons with the parietal region of the cerebrum. This explains the observation of Campbell,¹ that the degenerative changes associated with tabes dorsalis, finally progress into these central paths and also affect the cells of the post-Rolandic region.

Regarding the character of the sensations mediated by this area, it has been stated by Luciani and Seppilli that they subserve the muscle and cutaneous senses. But as pain is not felt as a result of the stimulation of this area, it may be said that it is chiefly concerned with muscular and tactile sensibility, and in a lesser degree also with the temperature sense. The fact that the perceptions and judgments based upon these sensations are mediated in the association realm of this region, is especially well betrayed by the diminution and loss of the stereoscopic acuity (astereognosis) invariably following lesions of this area. In other words, defects of the post-Rolandic region give rise to a more or less imperfect judgment of the shape and texture of objects when handled. Doubtlessly, therefore, this psychological difficulty must be dependent upon a loss of those associations which are ordinarily obtained with the help of the cellular units of this area. Another psychic defect frequently associated with injuries to this region, is tactile agnosia, *i.e.*, an inability to form judgments regarding the ordinary sensations of touch.

THE PSYCHO-VISUAL REGION

The Visual Center.—The fact that vision is under the control of a definite region of the cerebral cortex was discovered by Panizza in 1855. It was found that an injury to one posterior tip of the cerebrum of the dog gives rise to blindness in the opposite eye. This same observation was made subsequently by Hitzig (1874), but without knowing that it had already been called attention to previously. It was left to Munk (1878) to prove that the destruction of certain parts of the occipital lobes leads to total psychological or cortical blindness. These terms were used to indicate that the loss of vision is not due in this particular case to a functional uselessness of the retina or of the refracting media of the eyes, but to a central defect involving the perceptions and judgments pertaining to visual sensations. Omitting the controversial discussions arising in consequence of this discovery which were participated in by Goltz and Luciani, it may be stated in brief that the more recent experiments have fully substantiated these results of Munk.² Thus, Schaeffer (1888), Brown (1890), and

¹ Histol. Studies on Localization of Cerebral Functions, Cambridge, 1905.

² Über die Funkt. der Grosshirnrinde, Berlin, 1890, and Berliner Akad. der Wissenschaften, 1892-1901.

others, have shown that in the monkeys the ablation of the occipital lobes produces a permanent and total blindness. This result has also been obtained by Panichi (1895), with this difference, however, that the blindness can only be made permanent by extending the ablation somewhat beyond the commonly accepted boundaries of the occipital lobes.

With the exception of certain minor details, the visual center may, therefore, be said to be situated in the occipital realm of the cerebrum, and this conclusion is well borne out by the defects following the extirpation of only one of these lobes. Under this condition we obtain a blindness which is confined to the corresponding halves of the retinae, in other words, a bilateral hemianopia. The term of hemianopsia may also be used to indicate this condition, because it refers to a loss of vision in one-half of each visual field, while the former more directly applies to a loss of function of one-half of each retina.

The results of this operation, however, differ somewhat in different animals, but this should not surprise us, because attention has already been called to the fact that the fibers emerging through the optic nerve, do not pursue a uniform course. We have seen that they cross the mid-line completely in some animals and only partially in others. In the first instance, the ablation of the occipital cortex of one side must, of course, lead to a total blindness in the opposite eye. It seems advisable, however, not to extend this discussion unduly, but to confine ourselves to the conditions met with in man. We find here that the destruction of one occipital lobe is followed by disturbances in vision of hemiopic character, *i.e.*, by a bilateral homonymous hemianopsia. Thus, an injury to the left center produces a blindness in the outer half of the left and the inner half of the right eye, and a loss of vision in the opposite half of the visual field of each eye. Quite similarly, a lesion affecting the right center causes blindness in the two right halves of the retinae and left halves of the visual fields. This implies that the crossing of the retinal fibers is about equal. It is to be emphasized, however, that the foveae centrales are not involved, and hence, the field of direct and most acute vision is always excepted (Fig. 319). This peculiarity is explained by saying that the fovea centralis of each eye is connected with both centers, *i.e.*, the foveae are bilaterally represented.¹

Very peculiar types of blindness result if the lesion is situated in the course of the fibers connecting the retinae with the cortical center for vision. Thus, it must be evident that the destruction of one optic nerve must lead to a total blindness in the corresponding eye, while a lesion situated in the chiasma must produce bilateral defects in accordance with its location and extent. In a similar way, it may be inferred that the destruction of the central optic tract posterior to the chiasma must give rise to a hemianopia in the corresponding halves

¹ Sachs, *Der Hinterhauptlappen*, Leipzig, 1892; also: Laqueur and Schmidt, *Virchow's Archiv*, clviii, 1900, 466.

of the retinae. In many of these cases, however, a tertiary type of degeneration frequently results which involves certain neurons which are not directly affected by the primary lesion. This spreading gives rise to "sympathetic" effects, so that bilateral defects in vision may be obtained in spite of the fact that the original injury is confined to, say, one of the optic nerves and should, therefore, have produced blindness in only the corresponding eye.

Visual Association.—Upon genetic grounds it must be granted that the optic nerves are really not peripheral nerves at all, but true cerebral tracts, bearing a close resemblance to the lemniscus and other systems.¹ Hence, the retina must be regarded merely as an exposed feeler of the nervous system which is excited by the ethereal rays of light entering its substance. The impulses here generated are transferred to central parts over neurons, the cell-bodies of which are situated in the retinae. It is true, however, that the optic nerves also embrace a small number of centrifugal conductors which end in arborizations around certain elements of the retinae. The function of these fibers is not known. We have previously seen that the centripetal fibers of this tract connect with the superior colliculus, lateral geniculate, and thalamic nuclei, and that the psychovisual centers in the occipital realms of the cerebrum are more directly reached by way of the thalamo-geniculate bodies and the occipitothalamic radiations. In the course of the development of this cortical area, the importance of the lower visual centers formed by the aforesaid masses of gray matter, diminishes gradually. In the higher animals, the latter retain merely the function of ordinary relay stations for reflex action, while visual perception and memory are concentrated in the cortical area. In the simpler forms, such as the fish, these lower centers form the terminal stations of the optic tract and must, therefore, be capable to mediate in addition the psychical processes connected with vision.² It may be concluded, however, that the psychical activity of these animals is at best extremely rudimentary.

The psycho-visual area is composed of two fields, one being restricted to visual perception and the other to visual memory. Having reached the visual sphere, the retinal impulses are transferred to consciousness as perceptions which are then relegated to the memory field by way of association fibers. Stress has been placed upon the fact that the visual center cannot be restricted to a narrow sphere, although Henschen³ has stated that the visual paths of man terminate around the calcarine fissure on the mesial surface of the cerebrum. In support of this contention it has been mentioned that the examination of the brain of Laura Bridgman,⁴ the blind deaf-mute, has shown decided

¹ Parker, *Am. Nat.*, xlii, 1908, 601.

² Harris, *Brain*, xxvii, 1904, 106; also: Vincent, *Jour. Animal Behavior*, ii, 1912, 249.

³ *Brain*, xvi, 1893, 170.

⁴ Donaldson, *Am. Jour. of Psychol.*, 1892, 4.

atrophic changes in the region of the cuneus, which is situated above this fissure.

In addition, Flechsig¹ has proved by means of the myelinization method that the optic fibers terminate largely in the region situated along the calcarine fissure, *i.e.*, in the cuneus as well as in the gyrus lingualis. The same inference may be drawn from the clinical data compiled by Crispolti (1902), which show that the most permanent types of hemianopia result from lesions of this particular area.

The tendency, therefore, is to regard the cuneus as a more important area of the visual center than the lobulus lingualis and fusiformis. Besides these regions, however, which border upon the calcarine fissure, the psycho-visual sphere also embraces the three occipital convolutions and even encroaches upon the outlying districts of the parietal and temporal lobes. Evidently, the fields named last are set aside for visual memory. Any attempt, however, to localize these psychic areas more sharply must meet with failure. Thus, it does not seem correct to assume with Henschen and in accordance with the theory of Munk, that the retinal elements are projected in the visual center as individual units, because we are in no position to-day to support a contention of this kind by facts. This projection would imply that those elements which are situated in the upper area of the retina, are associated by the cellular units of the cuneus, while those situated below are associated by the lobulus lingualis. The point most frequently mentioned against such an almost mathematical subdivision of the visual center into visual units of definite value, is the fact that Monakow² and Bernheimer³ have shown that the fibers innervating the yellow spot, are widely scattered through the occipital cortex, and do not terminate in a circumscribed area of this region.

The Connection between the Visual Center and Others.—The fact that the stimulation of the occipital cortex gives rise to muscular movements, points toward the existence of definite anatomical connections between the visual center and the musculomotor mechanism. The stimulation of the upper surface of the right lobe causes the eyes to be turned downward and toward the left, while the excitation of its posterior region produces a deviation of the eyes upward and to the left. Furthermore, a purely lateral movement to the left may be evoked by stimulation of the mesial surface. It must be conceded, therefore, that the visual sensations are expressed in this case in accurate muscular movements, and that this end can only be attained by efferent impulses which traverse the occipitothalamic radiation and eventually find their way into the nuclei and distal ramifications of the third, fourth and sixth cranial nerves. It need scarcely be emphasized that connections of this kind also exist between this center and other motor paths.

¹ Sachs. Gesellsch. der Wissensch., 1904.

² Ergebn. der Physiol., 1907.

³ Archiv für Ophthalm., lvii, 1904, 363.

Visual perception and memory play an important part in all our reactions. This is well shown by the fact that lesions of the occipital region lead not only to hemianopia but also to psychical or cortical blindness. The latter condition, however, is not always complete, but may vary between a slight disturbance of our associations pertaining to a certain number of visual sensations, and an absolute inability on our part properly to recognize and rate all our visual impressions. In some animals, for example, certain lesions may be produced which permit sensations of sight as such to continue, while their ability to recognize and properly associate these impressions is lost absolutely. This constitutes true psychic blindness.

In man, this condition which is known as word-blindness, was first recognized in 1877 by Kussmaul.¹ It is characterized by an inability to comprehend printed or written words, without, however,

FIG. 346.—LATERAL VIEW OF A HUMAN HEMISPHERE; CORTICAL AREA V, DAMAGE TO WHICH PRODUCES "MIND-BLINDNESS" (WORD-BLINDNESS); CORTICAL AREA H, DAMAGE TO WHICH PRODUCES "MIND-DEAFNESS" (WORD-DEAFNESS); CORTICAL AREA S, DAMAGE TO WHICH CAUSES THE LOSS OF AUDIBLE SPEECH; CORTICAL AREA W, DAMAGE TO WHICH ABOLISHES THE POWER OF WRITING. (Donaldson.)

involving the faculty of expressing our thoughts by words or in writing. A person so afflicted is capable of seeing and even of copying the letters, but he has no associations pertaining to them. For this reason, they remain absolutely meaningless to him. He is, therefore, in the same position as a person who attempts to read a language with which he is not familiar, say Arabic or Chinese. The condition of word-blindness forces us to assume that the psycho-optical region embraces a circumscribed area which is set aside for the perception and memory of letters. As primitive man, in all probability, was not in possession of an association zone of this kind, it has been developed in the course of time. Its location has not been definitely established as yet, although those cases of word-blindness which have come to autopsy, have shown lesions in the second parietal convolution and gyrus

¹ Störungen der Sprache, 1885.

angularis of the left side. This area forms the outlying district of the memory realm of the psycho-visual region.

THE PSYCHO-AUDITORY REGION

The Auditory Center.—The first tangible data regarding the location of the auditory center, have been furnished by Ferrier in 1875. It was found at that time that the excitation of the surface of the temporal lobes gives rise to muscular movements involving the ear of the opposite side. Somewhat later, when these experiments were extended to include ablation of this particular area of the cerebral cortex, it was established that the destruction of both temporal lobes produces total deafness, while the ablation of only one lobe leads solely to an impairment of hearing. Subsequent experimentation by Munk (1878-81), Luciani and Tamburini (1879), and Bechterew (1887) has proved this localization to be essentially correct. In addition, it has been pointed out that the psycho-acoustic region embraces not only the temporal lobe but also the fields extending from here in the direction of the parieto-occipital convolutions and the gyrus hippocampi.

These outlying districts appear to be set aside for memory, while the chief area of this center seems to be restricted to the superior temporal convolution. This deduction is based upon the results of stimulation of the surface of the temporal cortex as well as upon the manner of distribution of the incoming fibers, as determined by the myelinization-method of Flechsig.¹ It seems that the fibers of the auditory radiation terminate chiefly in the superior convolution of this lobe (Monakow). This area also embraces a sphere for musical sounds.

The experiments of unilateral extirpation of the temporal lobes have also brought out the fact that the deafness resulting therefrom, is only temporary, and that the symptoms are chiefly confined to the ear of the opposite side.² This result strongly suggests a crossing of the auditory fibers which, as we have seen in an earlier chapter, takes place in the corpus trapezoideum. This decussation is incomplete and may, therefore, be likened to that occurring in the optic chiasma. Thus, it may be gathered that, in the dog, the organ of Corti in the cochlea is bilaterally represented. Besides this rather incomplete and temporary deafness, the destruction of the temporal cortex also gives rise to psychic or cortical deafness, which means that the animal hears the sounds, but is quite unable to understand them.

This condition has also been observed in persons who at autopsy showed characteristic lesions of the temporal cortex. They appeared to be able to hear even whispers, but could not comprehend their meaning. In analogy to word-blindness, Kussmaul (1876) designated this condition later on as word-deafness. Luciani and Seppilli localized the seat of this difficulty in the first and second temporal con-

¹ Neurol. Zentralblatt, 1903, 202.

² Tamburini, Revista di Freniatria, Reggio Emilia, 1903.

volutions of the left side. A person so afflicted is in the same position as one who is spoken to in a foreign language, *i.e.*, he hears the words, but is unable to depict their meaning, because he cannot properly associate them. Wernicke¹ recognized at an early date that this condition, together with word-blindness, must lead to a loss of speech, because individuals who thus fail in their associations, cannot react to auditory and visual impressions by the production of coördinated sounds. It may also be inferred that they cannot react to these impressions by the act of writing for the same reason. The latter condition is known as *agraphia*, and the former as *aphasia*.

THE CENTERS FOR SMELL AND TASTE

The Location of the Olfactory Center.—The sense of smell is very unequally developed. We have seen that it forms the dominant sense in many of the lower vertebrates; for example, in the fish in which almost the entire cerebrum is concerned with this function. These animals, however, are not in possession of a true cerebral cortex, the first indications of it appearing in the amphibia and reptilia. Other animals are entirely lacking in olfactory organs; for example, the dolphin, porpoise and whale.² This divergency enables us to divide animals into two groups, namely into *osmatic* and *anosmatic*, and the former again into *macrosmatic* and *microsmatic*. As examples of the first kind, might be mentioned the dog, rabbit, rat and opossum and as an example of the second kind, man.

The acuity of this sense is in keeping not only with the complexity of the olfactory cells in the nasal cavity, but also with that of the association area in the cortex. In the fish, the reactions following olfactory impressions, are still chiefly reflex. A true cortical or psychic element is first imparted to them in the amphibians and reptiles. This statement implies, that beginning with these animals, the olfactory reflex realm is gradually amplified by a cortical center. As far as man is concerned, this psycho-olfactory region has been localized by Ferrier in the gyrus hippocampi, and particularly in its distal limb, the uncus. This conclusion has been reached partly in accordance with the anatomical data pertaining to the distribution of the olfactory fibers, and partly because the stimulation of this area in monkeys produces movements involving the muscles of the lips and nostrils of the same side. This effect is similar in character to that produced by inhaling an irritating vapor. It should be remembered, however, that reactions of the latter kind are due chiefly to the excitation of the receptors of the trigeminus nerve. Luciani came to the same conclusions as Ferrier, but extended this area somewhat to include the subiculum cornu Ammonis. Bechterew,³ on the

¹ *Der aphasische Symptomenkomplex*, Breslau, 1874.

² Zwardemaker, *Ergebn. der Physiol.*, i, 1902, and Herrick, *Evolution of Intelligence and its Organs*, Science, xxxi, 1910, 7.

³ *Archiv für Physiol.*, 1899, Suppl., 391.

other hand, believes that Ammon's horn does not form a part of the olfactory area.

The Center for Taste.—The psychic area for the sensations of taste has not been definitely located as yet. As the taste buds are widely scattered, their excitation involves the seventh and ninth cranial nerves; in fact, Wilson¹ states that a few of these receptors are also situated in the mucous membrane of the larynx and epiglottis. The latter seem to be innervated by the vagus nerve. In the medulla these afferent fibers are intimately connected with the motor mechanism concerned in mastication and deglutition, as well as with the spinal nuclei. They terminate finally in the gyrus hippocampi near the anterior end of the temporal lobe. In fishes these fibers may be traced to the region of the hypothalamus.

THE CENTER FOR SPEECH

The Speech Circuit.—The psychic area for the associations required in the production of intelligent sounds and speaking, should, of course, not be confounded with that region of the cerebral cortex which has to do with the innervation of the muscles of the larynx and functionally allied structures and forms a part of the general motor area. In fact, these motor points are under the direct control of the psychic speech center. In the latter area the various revalent associations from the visual, auditory and other centers are brought together and are psychically adapted to speech. The speech center, therefore, is the seat of those memories which are required for the execution of the perfectly definite and coördinated movements necessary for speaking.

Sounds are a common phenomenon in nature. We cannot, however, concern ourselves at this time with the reflex-like production of noises, such as result in insects in consequence of the rubbing together of the legs or mandibles. The first indications of true associated sounds are present in amphibians and reptiles, but only in a rudimentary manner, because the cerebral cortex of these animals is largely concerned with olfaction. Such noises, however, as are produced by means of resonating pouches, seem to contain at least a slight cortical element. Somewhat higher in the scale of the Animal Kingdom this psychic admixture becomes unmistakable. Its increasing conspicuousness pursues a course parallel to the retrogression of the olfactory apparatus and the development of the association areas pertaining to other senses. Undoubtedly, this change is far advanced in the birds and is almost complete in the monkeys and apes. In the mammals, the production of sounds is universal and diversified, but the range of these sounds is relatively limited. In other words, the sounds which they produce are few in number, but are nevertheless made for very specific purposes. In this connection, brief reference might be made to certain seemingly authentic cases which suggest that it is possible

¹ Brain, xxviii, 1905, 339.

to train animals to produce a definite number of associated sounds. Instances of this kind are the "talking dog" and the "talking horse." The higher monkeys, it is said, are capable of uttering a few coördinated sounds in expression of particular mental concepts.

A true coördination of sounds in the form of speech, however, is shown only by man. This achievement is made possible very largely by the development of the association area pertaining to this function and not by a correspondingly much greater intricacy of the motor apparatus necessary for speaking. Already during infancy, man is equipped with a phonetic mechanism which is practically complete as far as its structural complexity is concerned, but is still in need of functional development. This it acquires

in the course of the succeeding years. This awakening of the associations concerned in speech, is one of the most interesting and instructive phenomena in the life of man. The primary cooing sounds of the infant are gradually amplified by a number of successive sounds having a definite meaning. This augmentation indicates an extension and melting together of intracerebral paths, so that various impressions from other association centers may be brought to bear upon speech. Once this union has been effected, the development of speech is much more rapid, being subject, of course, to differences in the training of the child.

FIG. 347.—THE SPEECH CIRCUIT.

R, Receptor; V, association center; C, center for speech; M, motor points for muscles of larynx; L, larynx.

Speaking is the outcome of certain mental processes; in other words, it is the result of particular afferent impulses which may enter the body by way of practically any receptor. They are then associated in the perception and memory realms of the corresponding regions of the cerebral cortex. As speech follows visual, auditory, tactile and other impressions, it may be said that these mechanisms are really tributary to the speech center. Hence,

speech is the product of a harmonious interaction between different peripheral and central nervous mechanisms. It is true, however, that these tributary complexes are not developed simultaneously but successively, and that training has much to do with their functional adaptability to speech. Thus, it is a common experience that the memory sphere of vision becomes functional at an earlier date than that of audition; at least, it seems more difficult for the infant to make the latter subservient to its speech requirements.

The morphological and functional arrangement of the adult mechanism of speech may be illustrated best in the form of a diagram. It has been said that speech is under the control of an association area situated in the cortex of the cerebrum (Fig. 347). This center stands in communication with the phonating organs, the larynx and allied

parts (*L*), by means of an efferent path through the motor area (*M*). This entire complex, inclusive, so to speak, of one-half of the center of speech, forms the motor arc of the speech circuit. But, inasmuch as speech results only in consequence of incoming impulses, inclusive of those of pure psychic origin, this circuit can only be completed by bringing it into relation with a sensory or afferent arc. The latter may embrace either the visual, auditory, or any other mechanism. Supposing that we are now dealing with a visual impression, we would say that the stimuli are received upon the retina (*R*) and are then conveyed to the visual center in the occipital cortex for proper association (*V*). From here they are conducted to the center of speech by way of definite association fibers. In the chief center they are then remodelled and transferred upon the efferent path by way of which they attain the larynx. Naturally, if speech is the outcome of an auditory impression, the organ of Corti and the auditory center would have to be substituted for the retina and the visual center, but the motor path remains the same.

The Location of the Center for Speech.

Aphasia.—Adult persons are capable of communicating their mental products to one another by means of mimic movements, speech and writing. The second of these means has been shown by Broca¹ to be lost whenever the base of the left inferior frontal convolution is extensively injured. For this reason, this investigator recognized in this area the cortical regulatory factor of speech, or more correctly speaking, of the motor apparatus which derives its innervation from the fifth, seventh and ninth to twelfth cranial nerves. He designated the aforesaid condition as cortical motor aphasia, thereby furnishing the basis for the commonly accepted view that the speech center is situated in the left inferior frontal convolution. We shall see later on that this localization is not quite correct, because it is restricted to too narrow a sphere. In this connection attention should also be called to the fact that cerebral localization should never be attempted upon a strictly anatomical basis. Function should really be the deciding factor.

The term aphasia signifies a loss of the power of speech (Fig. 348). An individual so afflicted is unable to express his ideas in spoken words. The difficulty, however, does not lie in the larynx nor in the paths con-

FIG. 348.—DIAGRAM OF THE SPEECH CIRCUIT, ILLUSTRATING THE POSITION OF THE LESIONS WHICH GIVE RISE TO SENSORY AND MOTOR APHASIA.

R, Receptor; *V*, association center; *C*, speech center; *M*, motor points; *L*, larynx; *SA*, realm of sensory aphasia; *MA*, realm of motor aphasia.

¹ In amplification of the observation of Bouillaud, 1825.

necting this organ with the cerebrum. This is shown by the fact that its movements during respiration, mastication and deglutition are executed with perfect precision, and may even be used for mimic expressions, singing and whistling. Aphasia, therefore, is an intracerebral defect involving the spontaneity or power of phonetic expression (Fig. 348). This implies that the aphasic person is no longer in a condition to express his thoughts in words which form his principal means of communication with his fellow-men. To be sure, man is also subject to a number of conditions in which the intellectual faculties are in abeyance, either from birth, as in idiots, or from disease, as in coma, stupor, dementia and certain states of hysteria. This type of speechlessness, although due to cerebral defects, cannot be classified as aphasia.

Motor aphasia is the result of an injury either to the efferent or motor realm of the speech center or to the path connecting it with the motor area situated along the fissure of Rolando. The motor area itself, however, is not affected in cases of pure aphasia, as is evinced by the fact that the muscles used in speaking are not paralyzed but have only lost their central directing influence. For this reason, we must think of the motor realm of the center of speech as a storehouse of those memories which are directly concerned with articulation and the phonetic construction of words. To be sure, an injury may be so extensive that it also involves the motor area, in which case the aphasia is associated with a hemiplegia. This is not at all uncommon.

It is possible to amplify these associations and to impart to them a specificity which in turn will tend to render the action of the laryngeal parts more and more effective. In other words, while the laryngeal parts may be fully developed, they cannot attain their greatest functional efficiency unless the association realm is trained and made to progress in a corresponding measure.

An injury to this center most frequently results in consequence of traumas and hemorrhages in the region of the middle cerebral artery. These lesions may be very extensive or more or less restricted; hence, the resulting motor aphasia or aphemia may be either complete or partial in character. In the former case, the person loses his power of speech absolutely, while in the latter he retains the faculty of uttering a limited number of words. Thus, Broca has described a person suffering from a loss of all numerical concepts with the exception of the term "three," this number being employed by him constantly in referring to all numerical values. Quite similarly, a person may lose the use of certain nouns and pronouns, or persistently employ words in wrong combinations (paraphasia). The point to be emphasized is that these defects in speech may be so specific that they may almost be compared to the loss of one of the strings of a piano or other musical instrument.

Another point to be noted is that the mental faculties of a person afflicted with motor aphasia, are generally preserved, provided, of course, that the injury is perfectly localized. This implies that his

power of associating the various sensory impressions is relatively normal, although he absolutely fails in his attempts to give verbal expression to these concepts. Indeed, a person of this kind may be told the missing words repeatedly without being able to utter them, for the reason that his power of forming words has been lost. It is true, however, that any statement which definitely asserts that there is no impairment of the intellectual faculties in motor aphasia, should be accepted with reserve, because aphasias unaccompanied by a lowering of other faculties are not common. A pure motor aphasia is designated as *aphemia*. The real determining factor of the loss of intelligence, associated with aphasia, is the cause and extent of the lesion, because it is more than probable that a degenerative process affecting the frontal convolutions, most generally passes beyond the confines of this region and also involves more distant areas of the cerebrum. Thus, while these patients may deport themselves reasonably well and even continue to transact ordinary business, their difficulty in speech is in many cases associated with others, such as an at least partial paralysis of the skeletal muscles, showing an involvement of the motor area (*hemiplegia*), or an *anarthria*, proving an impairment of the motor power of expression (*Marie*). The latter condition usually indicates a lesion of the white matter of the external capsule as its winds around the lenticular nucleus.

In many cases of aphasia, we also observe a loss of the power of writing (*agraphia*), or a loss of the power of making purposive movements of a familiar kind (*apraxia*). The latter condition may be tested by handing the patient a comb, drinking glass, matches, or other articles and noticing whether he knows how to use them. *Apraxia* may be sensory or motor in its character.

This discussion inadvertently leads us to the further consideration of the data supplied by Bouillaud and Broca in support of the contention that the speech center is located in the left inferior frontal convolution. It has been stated that this is true only in right-handed persons, *i.e.*, in about 95 per cent. of people, and that this center is situated on the right side in left-handed individuals (Noison, 1862). Moreover, it is a common experience that reëducation is difficult to accomplish in the adult, but not in children.¹ This fact seems to suggest that the destruction of the aforesaid area in children, allows the elements in the opposite frontal lobe to develop into a true center. Very difficult to understand are those cases which prove that aphasia may be present in an individual whose inferior frontal lobe was shown at necropsy to be free from lesions. Again, it has been demonstrated that aphasia may be absent in cases of undisputed destruction of Broca's area.² Montier presents the records of 108 trustworthy cases. Of these, 19 support Broca's contention, while 84 are against it. In 57 of them motor aphasia was present in spite of the fact that Broca's area was intact, while the others showed

¹ Gowers, *Diseases of the Brain*, London, 1885.

² Monakow, *Gehirnpathologie*, 1906, and Collier, *Brain*, 1908.

a destruction of this region, but no aphasia. It seems, therefore, that we cannot adhere to the old view of Broca, but must regard this particular area merely as a link in the chain of the speech circuit. As speech is a skilled act, involving several cerebral regions, Marie¹ believes that it cannot be referred to any particular group of cells to the exclusion of another. The latter point will be brought out more clearly during the succeeding discussion upon sensory aphasia.²

Sensory Aphasia.—Speaking, as well as writing, necessitates the presence of distinct concepts which may be memories of visual sensations, auditory sensations, tactile sensations and others. Hence, it may be gathered that speech must be lost whenever these associations are absent, because it then lacks its causative factors. In other words, a person may be in complete possession of the power of articulation and phonation, but be quite unable properly to construct those mental pictures or concepts which ordinarily give rise to speech. In this case, therefore, the difficulty lies on the sensory side of the speech circuit.

We have previously seen that an injury to Wernicke's area of the temporal lobe gives rise to word-deafness, *i.e.*, to an inability of correctly associating sounds or words, in spite of the fact that they are clearly heard. In the same way, a lesion to the parietal realm of the psycho-visual field may give rise to the condition of word-blindness, *i.e.*, to an inability of associating written or printed language. In both cases, of course, the peripheral afferent paths are in perfect condition, and hence, the difficulty must be situated in the auditory and visual centers. Under ordinary conditions, these two centers are the chief contributors to the speech center proper, but not in an equal measure, because the auditory realm is no doubt more directly associated with it than the visual. This is shown especially by the fact that a loss of speech is more frequently associated with word-deafness than with word-blindness. This constitutes the so-called sensory aphasia of Wernicke,³ so designated to differentiate it from the motor aphasia of Broca. A simple word-blindness, on the other hand, rarely leads to sensory aphasia, but presents itself rather as an inability to read (*alexia*) and an inability to write from copy (*agraphia*). It may happen, however, that the primary lesion does not remain confined to the psycho-optic realm but also involves the psycho-auditory field, in which case, of course, the aphasia is associated with both conditions, word-deafness and word-blindness, as well as with *alexia* and *agraphia*. It should also be added that auditory aphasia is often combined with at least slight defects in hearing, and visual aphasia, with certain defects in sight (*hemianopia*). This cannot surprise us, because the lesions involving these areas, are rarely so precisely placed as not to affect neighboring units.

¹ *Semaine médicale*, Nos. 21, 42 and 48, 1906.

² A. Meyer, *Harvey Lectures*, New York, 1910, 228.

³ *Der aphasische Symptomenkomplex*, Breslau, 1874.

Strictly speaking, however, the condition of sensory aphasia must result in consequence of any lesion producing a loss of the intellectual recognition of external objects through any one of our senses, at least, of those which ordinarily give rise to concepts employed in speech. On this account, the different association centers may really be regarded as subsidiary or tributary centers to the speech center. This failure of intellectual recognition has been designated as agnosia; hence, word-deafness is really auditory agnosia, and word-blindness, visual agnosia, while stereognosis is tactile agnosia. Thus, practically any agnosia may give rise to defects in expressing our ideas in words or deeds. The location and extent of these sensory lesions determine the intensity of the aphasia or agraphia; and hence, these conditions

FIG. 349.—THE SPEECH CIRCUIT PROJECTED TO SHOW THE LOCATION OF LESIONS WHICH MAY GIVE RISE TO APHASIA.

E, Eye; *V*, visual association area; *SC*, speech center; *M*, motor points; *L*, larynx. Sensory aphasia follows injuries to the association center (*A*) its transcortical connecting path (*B*) or the receiving side of the center for speech (*C*). Motor aphasia may be produced by an injury to the motor neurones of the center for speech (*D*) or its connecting path (*E*) with the motor area.

may be either complete or incomplete. At all events, sensory aphasics suffer in most instances a greater deterioration of their mental faculties than the simple motor aphasics, because their primary association spheres are more directly involved. For the present, therefore, we must adhere to the belief that the speech circuit consists of a number of distinct centers, the several activities of which are combined into the single product of speech. This circuit may be broken at different points, namely, at (*a*) the tributary association center, (*b*) the association path connecting this lower center with the chief center, (*c*) the chief center on its ingoing or sensory side, (*d*) the chief center on its outgoing or efferent side, and (*e*) the association path connecting the latter with the motor area. Injuries at points *a*, *b*, and *c*, must give rise to sensory aphasia and injuries at points *d* and *e*, to motor aphasia.

Agraphia.—As a second means of communicating our ideas to our fellow-men, we employ a code of written signals which are in no way less arbitrary than those of speech. They differ with the character of the language and hence, also with the intelligence of the people employing them. Like speech, writing is a skillful act and is controlled by a number of cortical centers. Both faculties are acquired and may be perfected by training. First of all, we observe that the muscles of the hand and fingers are controlled by certain units of the motor area. These in turn are under the guidance of a psychomotor area of the cortex which, as far as is known, occupies a position in or very near to the psychomotor center for speech. Secondly, as writing is the direct outcome of associative processes in different sensory regions of the cortex, the latter may be regarded as tributary areas to the chief psychomotor center.

Theoretically considered, therefore, we might recognize the existence of a distinct writing-circuit, similar in its outline to the speech circuit. In strict analogy to the latter, it might be said to possess a sensory and a motor side, the ingoing impulses being derived chiefly from the visual and auditory centers. While this conception is undoubtedly correct physiologically, no pathological cases have been recorded as yet which might prove the power of writing to be a separate cortical entity. In fact, the records show that agraphia or loss of the power of writing, is present only in connection with at least a slight degree of aphasia. This is also true of paraphasia, *i.e.*, the writing of wrong words, syllables and letters. Agraphia, however, is due to a lesion of those psychic centers which are directly concerned with the act of writing. Hence, writer's cramp is not an agraphia, but is due in all probability to a neurosis of psychogenic origin. Thus, this condition is comparable to those disturbances in speech which are classified as stuttering and stammering. Very characteristic defects in writing are exhibited in different psychoses. The paralytic writes carelessly, leaving out words and syllables, while the maniac writes very hastily and the katatonic in a peculiar stilted manner. It may be concluded, therefore, that speech and writing are closely related, acquired and educative faculties. Their motor centers, paths and end-organs are quite distinct, but on the sensory side we find that practically the same psychic areas are involved in the two processes. This fact accounts for the close relationship existing between agraphia and aphasia.

It has also been claimed by Kussmaul that our musical faculties are separately represented in the cerebral cortex. This implies that the psycho-visual and psycho-auditory regions embrace a circumscribed area in which musical symbols and sounds are associated. This conclusion is based upon the fact that the power of reading musical notes may be preserved in alexia.¹ A condition of amusia, however, has been repeatedly observed in consequence of cerebral lesions.

¹ Oppenheim, *Charité Ann.*, 1888, 345.

THE FRONTAL ASSOCIATION AREA

The preceding localization of the different motor and sensory areas has undoubtedly led us to believe that the cerebral cortex embraces a number of island-like fields which are concerned with particular functions. While this conception is correct, it should not be forgotten that still larger areas are situated in between those already explored, which have not as yet been shown to possess a specific functional value. Guided very largely by the fact that the aphasics may lose their power of word-formation without suffering a decided impairment of their intelligence, the clinicians have assumed that thought is quite independent of auditory, visual and other impressions and memories. In accordance with this assumption, it was then believed that the psycho-optic, the psycho-acoustic, and other psychic areas are apportioned severally to the different sense organs, and are amplified by definite areas in which solely the more general psychic activities are situated.

This at first purely hypothetical center of thought received a firmer morphological basis by the investigations of Flechsig¹ pertaining to the time of myelinization of the fibers of the embryonal brain. It is conceivable that those association areas of the cortex attain their function first which are first placed in possession of myelinated fibers, and thus antecede the others in gaining connection with the outgoing paths of the white matter. By this method Flechsig succeeded in outlining thirty-six different cortical fields which he further divided into *primary*, *intermediary* and *terminal*. The first attain their myelinated fibers at birth and constitute the primary sense centers, namely, those of smell, cutaneous and muscle sense, sight, hearing and touch. These areas are characterized by large numbers of radial, transverse and projection fibers which eventually make connection with the more distant projection centers apportioned to the different sensations and motor actions. The intermediary fields contain fibers which attain their medullary sheath during the first month of extra-uterine life. The terminal regions possess few transverse fibers, but numerous association paths which unite them with the different projection centers. They form the association areas which amplify the individual primary sensory centers and thus form the memory realms for vision, audition, olfaction, etc. In addition, they form those independent association realms which give rise to the higher psychic concepts. For this reason, they may be regarded as the organs of perception and thought. In this connection it should be stated, however, that many physiologists do not admit that the highest psychical activities are mediated by special and individualized association centers (Munk), but are produced in the association realms belonging to the different primary sensory regions.

¹ Die Lokalisation der geist. Vorgänge, Leipzig, 1896; also: Sächs. Gesellsch. der Wissensch., Leipzig, 1904.

Whichever view is accepted, it must be evident that these different association regions are used for purposes of synthetizing the sensory impressions into perceptions and concepts. In accordance with Flechsig, it may thus be held that the association areas are the places in which sense impressions are built up into organized knowledge, and where a complex mental image is formed of conditions in our internal and external world. Typical association regions are, of course, the parieto-occipital and frontal realms. Regarding the latter, little progress has been made. It has been stated by Bolton¹ that mentally deficient persons (amentia) exhibit a thinning of the cortex which is especially marked in the frontal region. These atrophic changes are also apparent in idiotic and demented persons; in fact, it is claimed that they bear a direct relationship to the degree of the idiocy. Moebius² calls attention to the fact that the laterobasal portions of the frontal lobes are strongly developed in mathematicians. Thus, the brain of Helmholtz showed a uniform massiveness, but especially in the region between the gyrus angularis and the gyrus temporalis superior.³ According to Guzmán,⁴ the gyrus angularis is very prominent in people who possess a special talent for music. Mills⁵ argues that the intellectual states are controlled by the frontal lobes, while Spitzka's⁶ observations rather tend to prove a predominance of the posterior association fields in intellectual men.

Cases of extensive destruction of the frontal lobes have been cited repeatedly. Most commonly, however, reference is made to that of a workman whose frontal lobes were extensively lacerated by the end of a crowbar, driven through his skull by a premature explosion of dynamite (1850). In all these instances a decided change in the character and intelligence of the individual was noted. The more recent observations of Phelps,⁷ Müller⁸ and Schuster,⁹ however, have shown that a deterioration or loss of the higher mental qualities does not always follow, although minor mental changes, such as weakness of the memory, insane desires, and depression, are usually present. In all those cases in which these symptoms were the result of circumscribed tumors (glioma), the removal of the growth was generally followed by a complete mental recovery. In this connection, mention should also be made of the experiments of Franz¹⁰ which have proved that the removal of the frontal lobes in cats and monkeys leads to the loss of habits previously formed by brief periods of training. The habits so lost,

¹ Brain, 1903, 215, and 1910, 26.

² Über die Anlage der Mathematik, Leipzig, 1900.

³ Hansemann, Zeitschr. für Psych. der Sinnesorgane, xx, 1899, 1.

⁴ Anat. Anzeiger, xix, 239.

⁵ Univ. of Pennsylvania Med. Bull., xvii, 1904, 90.

⁶ Med. Record, 1901, and N. Y. Med. Jour., 1901.

⁷ New York Med. Jour., lxi, 1895, 8.

⁸ Allg. Zeitschr. für Psychiatrie, lix, 1902, 830.

⁹ Psych. Störungen bei Hirntumoren, 1902.

¹⁰ Archives of Psychology, March, 1907.

may be relearned in about the same period of time. Long-standing habits, on the other hand, seemed to be retained, in spite of the injury to this lobe.

As far as the higher functions of the association regions are concerned, much work must still be done to obtain more definite data. For the present, we can go no further than to state that the cortex of the cerebrum is the seat of special sensory and motor projection areas which may be mapped out with varying definiteness. We are also fairly well acquainted with the sensory and motor paths leading to and away from these regions. Around and in between these primary cortical fields certain association areas are situated which are intimately connected with the centers to which they belong, and in turn also with one another. Their destruction affects first of all the particular sensory or motor function to which they are assigned, and secondly, the functional equilibrium of the cerebrum as a whole. This constitutes the so-called diaschisis effect of Monakow,¹ consisting in a disturbance of the dynamics of the cerebral processes as a whole which, however, is rather transitory in its nature.

It is conceived that the higher mental concepts are not the product of special areas of the cortex, but are the result of discharges of nervous energy from one center to another as well as to more remote regions of the body. This interaction of nervous energy gives rise to a complex product, the analysis of which is at present impossible. This constitutes the so-called dynamic theory of cortical function, in accordance with which the different sensory and motor centers of the cerebrum are to be regarded merely as fixed points of action of a complex system of neurons and not as independent generators of mental actions. The result of this reverberation of discharges through the nervous system depends in each case upon the number and kind of neurons involved. Thus, the higher cortical function results in consequence of the correlation of its different products, and cannot be ascribed exclusively to one or the other of its constituent areas.

THE CORPUS CALLOSUM

The cerebral hemispheres are connected with one another by three tracts of commissural fibers, namely, the anterior commissure, the fornix, and the corpus callosum. The most conspicuous of these is the corpus callosum which forms the floor of the great longitudinal fissure and may be brought into view by separating the hemispheres. The fibers composing this structure, do not enter the main paths of the internal capsule, but extend directly across from cortex to cortex. According to Ferrier,² Brown-Séquard,³ Koranyi,⁴ and others, its division at the point where it crosses the longitudinal fissure, is not followed

¹ Die Lokalisation des Grosshirns, Wiesbaden, 1914.

² Proc. Royal Soc., London, 1875.

³ Compt. rend. Soc. biol., 1887.

⁴ Pflüger's Archiv, xlvii, 1896, 35.

by motor or sensory defects of any kind. Mott and Schaeffer,¹ however, have shown that its stimulation gives rise to symmetrical movements on the two sides of the body. Moreover, there is sufficient experimental evidence at hand to prove a distinct localization of these

FIG. 350.—VIEW FROM THE FRONT OF A CORONAL SECTION OF AN ADULT BRAIN MADE THREE INCHES BEHIND THE FRONTAL POLE. (*J. Symington.*)

fibers, because their stimulation evokes successively movements of the eyes, head, trunk, shoulder, arm, fingers, hip, tail and foot.

Obviously, therefore, this commissure forms a connection between the two motor areas for the association of symmetrical points of these regions. This fact may be substantiated by the ablation of one motor

¹ Brain, xiii, 1890, 174.

area, when the excitation of the corpus will evoke movements on that side of the body which is still connected with the uninjured area. Although generally associated with idiocy and epilepsy, certain cases have been recorded by Wahler¹ which show that lesions of the corpus callosum in man give rise to a disturbance of the muscular movements. Liepman² describes cases in which dyspraxia existed without any apparent injury to the motor cortex, the inference being that this disorder resulted from defects in the power of conduction of the corpus.

THE BASAL GANGLIA

The Corpus Striatum.—The nuclei caudati and nuclei lenticulares, constituting the corpora striata, are intimately connected with the frontal cortex by the corticocaudal bundle as well as with the thalamus, red nucleus, and through the latter with the longitudinal bundle. They form, therefore, important relay stations upon these paths and mediate reflexes of the more complex kind. In the lowest vertebrates, these bodies form almost the entire telencephalon and really serve as the basal stem from which the hemispheres of the higher animals are developed. Their importance seems to be greatest in the birds, because the more complex processes of these animals appear to be mediated by these bodies, rather than by the pallium, or hemispheres.

The question whether they possess an independent function, cannot be answered with certainty, because their destruction by means of injections of chromic acid, as well as their stimulation, has yielded very conflicting results. Their close connection with the internal capsule makes a direct involvement of these paths not improbable, and hence, many of the effects described by earlier investigators³ may be due to this cause. It seems to be established, however, that these ganglia are closely associated with heat production and the regulation of the body temperature,⁴ because their stimulation invariably results in a rather lasting rise in temperature, amounting to as much as 1.6° C. Mayer and Barbour have substantiated these results by permitting warm and cool water to flow upon these bodies. Cooling the water produced shivering and a rise in the body temperature, while warming it lowered the body temperature.

THE THALAMUS OPTICUS

This body consists of three parts, known as the median, lateral, and anterior nuclei. It is intimately connected with the corpus striatum and the cerebral cortex by ingoing and outgoing fibers, and also forms the end-station of the secondary sensory tracts of the spinal cord

¹ Balkentumoren, Leipzig, 1904.

² Med. Klinik, 1907, 725.

³ Schüller, Zentralbl. für Physiol., 1902, 222.

⁴ Jto., Archiv für Physiol., 1898, 537, and Zeitschr. für Biologie, xxxciii, 1898, 36; also Nicolaides and Dontas, Archiv für Physiol., 1911, 249.

and medulla oblongata. In addition, its pulvinar prominences, together with the lateral geniculates and anterior corpora, form the end-station of the primary division of the optic tract, while the median geniculates and posterior corpora receive the auditory tract. It is also connected with the cerebellum, and sends a few fibers to the red nucleus and medulla oblongata.¹

In accordance with its connections with the cutaneous, sensory, optic and auditory tracts, Monakow² regards the thalamus opticus, together with the lateral and median geniculates, as a subsidiary cerebral cortex, the purpose of which is to transfer these sensations to the proper association areas. Lesions of this body, therefore, must give rise to very diverse symptoms: This also holds true of the outgoing impulses. Bechterew,³ for example, calls attention to the loss of the emotional movements concerned with laughing and crying, and the impairment of the mimic play of the facial muscles. This investigator also states that this body contains the reflex center for the secretion of the tears. Its activation also produces a dilatation of the pupils, a bulging of the eyeballs and a retraction of the eyelids. Injury to this body also gives rise to the so-called phenomenon of Romberg, *i.e.*, to an inability to stand erect when the eyes are closed. This symptom serves as a diagnostic sign in tabes dorsalis and other degenerative affections of the nervous system.⁴

THE CORPORA QUADRIGEMINA

The anterior corpora receive a part of the optic fibers and direct them to the cortex of the occipital lobes. The posterior corpora, together with the median geniculates, serve as end-stations of the secondary auditory fibers, and communicate with the cortex of the temporal lobes and other parts of the cerebrum. In the lower forms, the destruction of these bodies occasions blindness in both eyes, while their unilateral laceration gives rise to blindness either in the corresponding eye or in that of the opposite side. This diversity in the effects is caused by differences in the crossing of the optic fibers. In the monkeys and man, blindness does not result,⁵ for the reason that the loss of these relay stations is compensated for by a transfer of their optic impulses to other tracts.

The anterior corpora contain the center for the constriction of the pupils, the impulses being transferred in this place from the optic tract to that of the oculomotor. Furthermore, this transfer is distinctly reciprocal, because the stimuli brought to bear upon the retina of one

¹ Wallenberg, *Neurol. Zentralblatt*, xx, 1901, 50.

² *Gehirnpathologie*, Wien, 1904.

³ *Neurol. Zentralblatt*, x, 1894, 481.

⁴ Wilbrand and Sanger, *Die Neurologie des Auges*, Wiesbaden, 1904; also Sachs, *Brain*, i, 1909.

⁵ *Deutsche Zeitschr. fur Nervenheilkunde*, xvii, 1900, 428.

eye, affect both pupils in a corresponding degree. It need scarcely be emphasized, therefore, that the occipital cortex may be removed without destroying the light-reflex. An injury to the posterior corpora produces deafness in some animals, but not in monkeys.¹ These bodies also exert an inhibitor influence upon reflex action and are concerned with the orderly execution of movements. This is true especially of fishes, amphibians and reptiles, in which animals these functions are centered in the corpora bigemini, also known as the optic lobes.

¹ Ferrier and Turner, *Brain*, cciv, 1900, 27.

SECTION XIX

THE CEREBELLUM. THE PROTECTIVE MECHANISMS OF THE NERVOUS SYSTEM

CHAPTER LVII

THE CEREBELLUM

The Structure of the Cerebellum.—Anatomists have been accustomed to divide this organ into a median lobe or vermis and a right and left lateral lobe, or hemisphere. Bolk,¹ however, does not recog-

FIG. 351.—VIEW OF CEREBELLUM FROM BELOW. (J. Symington.)

nize this transverse arrangement, but advocates a division in the anteroposterior direction. Thus, it is stated that the sulcus primarius separates this organ into an anterior and a posterior portion. The former embraces the superior vermis, the monticulus and lobus quadratus anterior, while the latter includes the remaining portion of this organ, namely, the lobulus simplex, lobulus medianus posterior (vermis inferior) and the lobuli complicati.

¹ Das Cerebellum der Säugetiere, Jena, 1906.

The external surface of the cerebellum presents numerous deep furrows or sulci which limit narrow leaf-like gyri or convolutions. Thus, when cut transversely across, the section presents a number of lamellæ, or leaf-like subdivisions, which bear a close resemblance to the sprigs of the evergreen cedar tree, designated as *arbor vitæ*. Each lamella is made up of a central core of white matter and an external envelope of gray matter. The latter consists of three layers. At the point of contact between the cortical gray and the white matter lies a broad zone of very minute granular cells. These elements possess a scanty amount of cytoplasm and very short claw-like dendrites. Their axones are thin and non-medullated, and connect with the constituents of the superficial molecular layer. Here they divide into two branches which pursue a course parallel to the longitudinal axis of the lamellæ and terminate among the dendrites of the cells of Purkinje,¹ composing the

FIG. 352.—MEDIAN SECTION OF THE WORM.

Sagittal section of the cerebellum to show its internal structure, the relative depth of the fissures, and the grouping of the laminae. (Schäfer.)

central layer. The cells just mentioned are the most characteristic constituents of the cerebellar cortex. They present large pear-shaped bodies and a bushy fan-shaped network of dendrites, which is directed transversely to the long axis of the lamellæ. Their axons are myelinated and form the chief efferent path between the cortex of the cerebellum and the more deeply seated nuclei, to be described later. The most external zone is known as the molecular. It is occupied by the dendrites of the cells of Purkinje and those of the cells of the granular layer. A few neurons are interposed in this place for purposes of association. The most characteristic of these are the so-called basket cells.

The fibers composing the white matter are of three kinds—two afferent and one efferent. The former pass either directly into the molecular layer where they terminate among the dendrites of the cells of Purkinje, or extend only as far as the

¹ Named after their discoverer, Johannes Purkinje, Professor of Physiology at Breslau, from 1822 to 1850.

cells of the granular layer. The long ascending ones are known as tendril fibers and the short ones as moss fibers, so-called on account of the peculiar thickenings which they exhibit close to their points of termination. Ramon y Cajal believes that the tendrils are the terminals of the fibers of the middle peduncle, while the moss fibers are derived from the afferent fibers of the inferior peduncle. The efferent fibers are formed by the axons of the cells of Purkinje. They end in the deep nuclei, whence their impulses are conveyed onward by secondary neurons.

FIG. 353.—SECTION OF CORTEX OF CEREBELLUM.

a, Pia mater; *b*, exterior layer; *c*, layer of cells of Purkinje; *d*, inner or granular layer; *e*, medullary center. (Sankey.)

FIG. 354.—A PURKINJE CELL OF THE CEREBELLAR CORTEX. GOLGI METHOD.

a, Axon; *b*, collateral; *c*, *d*, ramifications of dendrons. (Cajal.)

The cerebellum also contains certain collections of gray matter beneath its cortex. Within the vermis and above the fourth ventricle are found the so-called roof ganglia, consisting of the nuclei fastigii situated near the middle line, the nuclei emboliformes located in a dorsal direction from the former, and the nuclei globosi. Directly embedded in the white matter of the hemispheres are the deep nuclei of which the nuclei dentati are the most conspicuous. As has been stated above, the latter form stations upon the efferent paths, and the former stations upon the afferent paths. Each incoming fiber divides into many branches and is thus brought into relation with the greatest possible number of cells of the granular layer.

The peculiar position of the latter toward the cells of Purkinje gives rise to very close and multiform synapses so that the widest possible ramifications are established. Functionally, this intricate union of the different neurons greatly facilitates the spreading and summation of impulses, and leads to the so-called avalanche conduction, *i.e.*, to an unusually extensive involvement of neurons.

The Connections of the Cerebellum.—The cerebellum is expanded upon a central stem formed by its three connecting strands of fibers, which are known as the superior, middle and inferior peduncles.

FIG. 355.

FIG. 355.—BASKET-WORK OF FIBERS AROUND TWO CELLS OF PURKINJE.

a, Axis-cylinder or nerve-fiber process of one of the corpuscles of Purkinje; *b*, fibers prolonged over the beginning of the axis-cylinder process; *c*, branches of the nerve-fiber processes of cells of the molecular layer felted together around the bodies of the corpuscles of Purkinje. (*Cajal*.)

FIG. 356.

FIG. 356.—FIGURE SHOWING THE THREE PAIRS OF CEREBELLAR PEDUNCLES.

On the left side the three cerebellar peduncles have been cut short; on the right side the hemisphere has been cut obliquely to show its connection with the superior and inferior peduncles. The cut ends of the cerebellar peduncles have been artificially separated from one another and are displayed diagrammatically. 1, Median groove of the fourth ventricle; 2, the same groove at the place where the auditory striæ emerge from it to cross the floor of the ventricle; 3, inferior peduncle or restiform body; 4, funiculus gracilis; 5, superior peduncle: on the right side the dissection shows the superior and inferior peduncles crossing each other as they pass into the white center of the cerebellum; 6, lateral fillet at the side of the pedunculi cerebri; 7, lateral grooves of the pedunculi cerebri; 8, corpora quadrigemina. (*From Sappey after Hirschfeld & Leveille.*)

The *superior peduncle* is made up very largely of fibers which arise in the dentate nuclei and pass toward the region of the midbrain. They cross the midline below the corpora quadrigemina and connect with the red nucleus and the optic thalamus. The afferent fibers of this peduncle are few in number and seem to be derived from the thalamus.

The *middle peduncle* is made up chiefly of afferent fibers which are derived from the nuclei of the pons. They cross the midline within this structure and pass into the lateral cerebellar hemisphere of the opposite side. A certain number of fibers also extend efferently from the cerebellum into the same region of the pons. In this way, a connection is formed with the corticopontine fibers which brings the cere-

bellum into relation with the cortex of the frontal and parietal lobes of the opposite side. The middle peduncle also embraces efferent fibers which are derived from the cells of Purkinje and, after their decussation in the pons, descend in the lateral funiculus of the cord. They eventually terminate around the motor cells of the anterior horns.

FIG. 357.—DIAGRAM OF THE CHIEF AFFERENT TRACTS LEADING INTO THE CEREBELLUM. (Herrick.)

The *inferior peduncle* is composed principally of afferent fibers which take their origin either in the spinal cord or in the bulb. The former constitute the continuation of the direct cerebellar tract and ascend through the corpus restiforme into the vermis of the cerebellum.¹ We have seen that this tract includes the axons of the

FIG. 357a.—DIAGRAM OF THE CHIEF EFFERENT TRACTS LEADING OUT OF THE CEREBELLUM. (Herrick.)

cells of Clark's column and collaterals from the posterior roots of the cord. The medullary fibers form the continuation of the vestibular division of the auditory nerve and connect the nuclei of Deiters and Bechterew with the nucleus fastigiatus

¹ Thomas, *Le Cervelet*, Paris, 1897.

and nucleus globosus of the cerebellum. In this way, this organ is brought into relation with the semicircular canals of the internal ear. It also receives a few fibers from the trigeminus, vagus and accessory nerves. The efferent fibers of the inferior peduncle arise in the dentate nucleus and form the direct anterolateral bundle which connects with the spinal tracts.

The Ablation of the Cerebellum.—The size and complexity of the cerebellum differ greatly in different animals. It reaches its highest development in the apes and man. In these animals we also find the greatest relative development of the cerebrum, although these organs do not display a perfect structural correspondence. We have seen that the cerebral cortex is made up of complexes of neurons which show very decided differences in their structure and arrangement, and mediate different nervous processes. The cerebrum, therefore, presents unmistakable evidence of a division of function. A precise localization of this kind is not in evidence in the cerebellum. On the contrary, this organ exhibits a decidedly homogeneous structure, and hence, we cannot go wrong in assuming that it possesses a single specific function. The correctness of this conclusion will become more apparent later on.

While repeated attempts have been made by Rolando (1809), Flourens (1824), Magendie (1825), Vulpian (1866), Nothnagel (1876), and others, to apply to the cerebellum the methods previously used in experiments upon the cerebrum, the results have proved very unsatisfactory on account of the difficulties which surgical interferences with this organ must necessarily be confronted by. Subsequent to the time of Galvani and Volta, when an undue stress was placed upon the electrical phenomena in nature, it was believed that the cerebellum supplies the "nerve force" which is required for our bodily processes. No doubt, this now ridiculous contention was based chiefly upon the observation that the lamellated outline of this organ in cross-section presents certain characteristics which remind one of the Voltaic pile. Later on Gall advocated the hypothesis that it is concerned with the sexual emotions. The first tangible view of its function was presented by Flourens, who regarded it as an organ for the coördination of muscular movements and particularly of those concerned in locomotion and the preservation of the equilibrium.

This view is widely accepted to-day and finds its origin in the array of symptoms displayed by pigeons whose cerebellar hemispheres have been removed either in part or in their entirety. Birds, in particular, are closely dependent upon a properly balanced muscular apparatus, inclusive of its central coördinating mechanism, the cerebellum. It may be inferred, therefore, that the excessive development of this organ noted in these animals, is in keeping with their muscular power, and that its removal must give rise to especially disturbing symptoms. Thus we find that a pigeon deprived of its cerebellar hemispheres, shows a spasmodic position of the wings, legs and head which renders standing, walking and flying impossible. Any attempt to

make it move results in excessive and asymmetrical muscular contractions which make it tumble in all directions. It is to be noted, however, that this loss of the power of coördinated movement is not caused by a paralytic condition of the different muscles but by an inability to correlate their actions for the attainment of a particular purpose. This swaying, staggering behavior constitutes the condition of ataxia. It is true, however, that these symptoms are not permanent, but gradually disappear in the course of time until merely a certain unsteadiness in the gait is left behind. In reptilia and amphibia the cerebellum is rudimentary. It cannot surprise us, therefore, to find that its ablation produces no noticeable defects in these animals.

Luciani¹ has extended these experiments to the mammals. He states that a dog, after unilateral removal of the cerebellum, shows a rigidity of the extremities, a curvature of the spine toward the operated side (opisthotonos), a deviation of the head toward the normal side, a slight nystagmus, and strabismus. The latter condition presents itself as a deviation of the eyes downward and inward on the operated side, and upward and outward on the normal side. Among the dynamic symptoms are mentioned atonia, or loss of the tonus of the musculature, asthenia, or loss of force, astasia, or loss of steadiness, and ataxia, or loss of the purposeful action of the musculature. These defects are chiefly unilateral and produce forced movements toward the abnormal side.² The latter consist in rolling motions toward the injured side as well as in movements in a circle toward the same side. Most generally, however, the more intense symptoms disappear in the course of from eight to ten days and are superseded by tremors. The general character of these defects as well as their rather short duration, led Luciani to assume that the cerebellum is an organ which by processes that remain below the threshold of consciousness, produces a reinforcement of the activity of the musculomotor centers. In this belief, however, he merely followed the views of du Petit (1710), Lafargue (1838), and others.

A number of cases are on record of inherited defects of the cerebellum in man, as well as of tumors which in the course of time destroyed large segments of this organ.³ The symptoms noted in these persons, show a decided similarity to those observed in the lower mammals. Briefly stated, cerebellar disease produces a condition of asynergia, *i.e.*, an inability properly to associate movements of greater or less complexity into functionally definite acts. If we adhere to this view, that the cerebellum is the seat of synergia, this organ assumes a position very similar to that of an association center of the cerebrum. It then becomes the center for the coördination of all muscular activity by reason of its power of associating those sensory impulses upon which movements depend.

¹ Arch. ital. de Physiol., xxi, 1894; Fisiol. et Pathol. del Cervelletto, Padova, 1897, and Ergebn. der Physiol., iii, 1904, 259.

² Eckhard, Herrmann's Handb. der Physiol., ii, 1883, 102.

³ Mills and Weisenburg, Jour. Am. Med. Assoc., Nov. 21, 1914.

The asynergia developed in the course of cerebellar disorders, presents itself in various forms, namely, as:

(a) *Hypermetry*, or *dismetry*, *i.e.*, a faulty measurement of the movements. In this particular instance, the patient is unable to associate the motor constituents of such acts as putting the index finger to the tip of the nose when the eyes are closed. Invariably, the finger misses its mark by a distance which increases with the degree of the hypermetry.

(b) *Adiadochokinesis*, or an inability to produce fine motor associations of an antagonistic character. This is shown by the fact that the patient is quite unable to pronate and supinate the hand when the forearm is flexed upon the arm.

(c) *Tremors*, shown in grasping for objects or in walking. The gait is trunkal, *i.e.*, the trunk constantly leaves its accustomed position, but is immediately supported in its new place by the legs in a stilt-like, sprawling manner. The cerebellar patient, however, knows his difficulty and makes compensatory movements to counteract these forced movements. In this regard he differs very decidedly from a person who is under the influence of alcohol. The latter reels in any direction without, at least in the final stage, being able to antagonize his movements. This loss of compensation is due, of course, to the fact that the alcohol has rendered the cerebral centers inactive. Cerebellar defects, on the other hand, need not be accompanied by cerebral depression. The cerebellar patient also exhibits an asynergia of the tongue and laryngeal muscles which gives rise to a jerky and crackling speech. The head is generally carried in the plane of the trunk. The eyes are seldom at rest.

(d) *Atonia*, or loss of tonus and relaxation of the muscles. This condition is dependent upon the fact that the tonic impulses from the cerebral cortex cannot become effective when the movements are asynergic.

(e) *Asthenia*, or loss of force. This condition is due to the exhaustion which results whenever the efforts to perform purposeful movements can no longer be properly controlled.

(f) *Astasia*, or loss of steadiness.

(g) *Ataxia*, or loss of the purposeful action of the muscles. This is a complex symptom resulting in consequence of the other defects.

Cerebellar Localization.—It has been shown by Ferrier that the stimulation of the surface of the hemispheres of the cerebellum or of its superior vermis, gives rise to movements on the same side of the body. In order to evoke these motor results, it becomes necessary to use much stronger stimuli than are ordinarily required for the excitation of the cortex of the cerebrum. This observation is in keeping with the histological arrangement of the cerebellar neurons, because the cortex is really the end station of the afferent paths, while the efferent paths as such begin in the more deeply seated nuclei.

Naturally, when we speak of localization of function in the cerebellum, we realize that this organ, contrary to the cerebrum, mediates only one kind of activity, namely, that of coördinating the movements of skeletal muscle. Thus, the only question before us is, whether different muscles or groups of muscles are controlled by different regions of this organ. That such a division of labor actually exists, has been shown very clearly by the experiments of Horsley and Clarke¹ which yielded movements of the eyes and head on excitation of the roof nuclei, and movements of the trunk and limbs on stimulation of the para-

¹ Brain, xxviii, 1905, 13.

cerebellar nuclei (Deiters'). Very similar results have been obtained by destroying circumscribed areas of the cerebellar cortex. Thus, it has been observed by Ryerberk¹ that the excision of the lobulus simplex produces forced movements of the head (head-nystagmus), a condition which is caused by a faulty control of the muscles of the neck. Quite similarly, the destruction of the ansiform lobule next to the crus primum, gives rise to a disordered action of the muscles of the foot of the same side, while lesions of the crus secundum cause a disturbance in the movements of the foot. In accordance with the older

FIG. 358.—DIAGRAM ILLUSTRATING CEREBELLAR LOCALIZATION.

A, Upper surface and B, lower surface of human cerebellum; *PrF*, primary fissure; *PcF*, postcleval fissure; *GLF*, great longitudinal fissure; *GHF*, great horizontal fissure; *PF*, pyramidal fissure; *ACL*, anterior crescentic lobe; *SSL*, superior semilunar lobe; *JSL*, anterior semilunar lobe; *BL*, biocentral lobe.

be considered as proof that such a minute localization does not exist.

The Function of the Cerebellum.—The foregoing data pertaining to the ablation and excitation of the cortex and intrinsic nuclei of the cerebellum, have been employed repeatedly as a possible basis for a more precise doctrine regarding the function of this organ. But while the general activity of this organ is clearly discernible, physiologists have not succeeded as yet in detecting the precise nature of the mechanism by means of which it is able to consummate its action. It has been stated above that Flourens regarded this organ as a center

¹Ergebn. der Physiologie, vii, 1908, 643, and xii, 1912, 533.

²Brain, xl, 1918, 461.

for the coördination of voluntary movements, while Rolando (1809), Weir Mitchell (1869), and Luciani considered it as an organ for the reinforcement of the activity of the musculomotor centers of the cerebrum and spinal cord. Munk ascribed to it the function of preserving the equilibrium of the body, while Hitzig saw in it the association center of the muscle sense. The last view has been advocated more recently by Lewandowsky¹ and Sherrington.

In last analysis we are dealing here with a reflex or excitomotor function of the cerebellum, in consequence of which the musculature of our body is forced to act within perfectly definite channels. We obtain an absolutely set condition of tonus, a certain amplitude of contraction, and a coördination of the activities of the different muscles. Thus, the only factor to be determined as yet is the intrinsic stimulus which causes the cerebellum to discharge these regulatory impulses. In the nature of this process, the latter may be either acceleratory or inhibitory.

In accordance with the view of Lussana, Hitzig and Lewandowsky, the cerebellum is to be regarded as the center for the muscle-sense, in which the different centripetal impulses from these sense organs are associated to give rise to coördinated motion. This association, however, does not involve consciousness, as does the association taking place in the cerebral centers, but remains subconscious, or more correctly speaking, reflex in its nature. Sherrington has gone a step farther and designates this organ as the head ganglion of the proprioceptive system, in which the different impulses from the muscle-spindles and from the labyrinth are brought together and associated subconsciously. From here the resulting impulses are conveyed through the superior peduncle into the cerebrum, where they influence the function of the motor areas. Other impulses are made to travel outward by way of its connections with the pons and bulb, and to direct the activity of the distant musculature. In this way, a complex mechanism is established which is concerned with the coördination of the musculature in general, but more particularly with that having to do with the maintenance of the equilibrium of the body as its position in space is changed to suit particular purposes.

¹ Archiv für Physiol., 1903, 129.

CHAPTER LVIII

THE PROTECTIVE MECHANISMS OF THE NERVOUS
SYSTEM

SLEEP AND NARCOSIS

The Enveloping Membranes.—The encephalon is contained in a rigid box formed by the cranial bones. The periosteal lining of the latter is displaced by the *dura mater*, a strong fibrous membrane which is lined internally with endothelial cells, and sends firm partitions inward for the support and protection of the different parts of the brain. A membranous process of this kind invades the great longitudinal fissure separating the hemispheres of the cerebrum. It is called the *falx cerebri*, because it possesses the shape of a sickle, being narrow in front and broad behind. Another, the *tentorium cerebelli*, extends transversely across between the cerebrum and cerebellum, while a third, the *falx cerebelli*, dips into the fissure between the cerebellar hemispheres. In several places, the *dura mater* is split into two layers for the reception of the sinuses which return the blood from the brain. In the spinal canal, the *dura* is not attached to the bone, but forms a long extended sac which closely invests the spinal cord and is held in place by the prolongations which pass outward to invest the individual spinal roots. Its outside surface is covered with networks of veins.

Directly underneath the *dura* and in intimate contact with it, lies a delicate transparent membrane, known as the *arachnoid*. Its outer surface is covered with endothelial cells and borders upon the subdural space which, in reality, is of capillary size and does not seem to have a special functional significance. Its under surface is placed in relation with the *pia mater*, but in such a way that a distinct cleft arises between them which is known as the subarachnoidal space. The latter is intersected by fine fiber connections and septa of connective tissue, the meshes of which are filled with a lymph-like fluid. It becomes especially conspicuous over the different sulci for the reason that the *pia mater* follows the surface of the brain into these furrows, while the *arachnoid* and *dura* pass directly across them in the form of bridges. In certain localities, however, the subarachnoid space is much increased in size, forming here the so-called *cisternæ* which in turn are connected with one another by delicate canals. Reflections of the *arachnoid* frequently dip into the fissures. One of these is found between the cerebral hemispheres and the third ventricle, where it extends into the lateral ventricle, becoming covered on one side by the *ependyma* of this cavity, and, on the other, by the *ependyma* of the roof of the third ventricle. It envelops a rich network

of blood-vessels forming the choroid plexus. A similar vascular fringe is suspended from the roof of the fourth ventricle.

This subarachnoid system is in direct communication with the ventricles of the brain by way of the foramen of Magendie and the foramina of Luschka. It also connects with the lymphatic spaces accompanying the cranial nerves, as well as with the central canal traversing the commissure of the gray matter of the spinal cord. In addition, it is placed into relation with the venous sinuses by the Pacchionian bodies. The latter are pouch-like protrusions from the surface of the arachnoid formed by enlargements of the normal villi of this membrane. Most of these bodies are lodged in irregular pits

FIG. 359.—TRANSVERSE SECTION THROUGH THE LONGITUDINAL FISSURE TO SHOW THE RELATION OF THE CEREBRUM TO THE MENINGES.

C.C., Corpus callosum; *W*, white matter; *G*, cortical gray matter; *P*, pia mater closely investing it; *A*, arachnoid with its membranous prolongations forming the subarachnoid space (*S.S.*); *D*, dura mater; *B*, skull consisting of the external and internal plates separated by a spongy center; *F*, falx cerebri enveloping *LS*, the longitudinal sinus. Into the latter extend the Pacchionian bodies.

in the calvaria, but some of them also project into the sinuses. They are particularly numerous along the superior longitudinal sinus. The close contact which is thus established between the liquid filling this entire system and the venous blood, might lead us to suppose that these saccules serve as a means for returning some of the liquor to the blood. They do not, however, constitute perfectly open outlets, and hence the escape of the lymph must be brought about very largely by processes of filtration and osmosis.

The Growth of the Brain.—Broca¹ states that the weight of the pia mater amounts to:

¹ *Elements d'Anthropologie générale*, 1885.

45 grams in individuals between the ages of 20-30

50 grams in individuals between the ages of 30-40

60 grams in individuals between the ages of 50-60

The capacity of the ventricles is 26 c.c., and the specific gravity of the entire encephalon 1.036. Its weight varies considerably even when members of the same race and social standing are compared. Thus, the compilations of Marshall¹ which are based on the records of Boyd, show immediately that the male possesses a heavier encephalon than the female and that all its subdivisions are heavier. Furthermore, a comparison of individuals of the same sex and age will show that those having the greater stature, exhibit a greater brain weight, and that the weight decreases with advancing years. This decrease in weight is most clearly indicated between the seventy-first and ninetieth years.

Vierordt² has collected a series of observations illustrating the changes in the weight of the brain between birth and the twenty-fifth year, which show that the greatest increase takes place during the first year. It grows rapidly to the fourth and fifth years, and then more gradually to the seventh year. From this time on its growth is very slight up to maturity. Social environment may be expected to be of influence, because the least favored individuals in any community usually show a certain retardation. The observations of Manouvrier have proved, however, that the average weight of the brains of murderers permits of no conclusions when compared with the average weight of the brains of the usual inmates of hospitals. Moreover, with the exception of the microcephalics, the insane as a class are not characterized by an especially slight brain weight. The examination of the brain capacities of a series of skulls belonging to different races, favors the western Europeans.³

The total number of neurons present in the central nervous system, has been estimated at 13,000,000,000. This estimate is based upon the records of Hammarberg,⁴ which in accordance with Thompson,⁵ give 9,200,000,000 well-marked cell-bodies to the cortex of the cerebrum alone.

The Cerebrospinal Fluid.⁶—The subarachnoid and subdural spaces, as well as the encephalic ventricles, are filled with a colorless liquid, the quantity of which varies between 60 and 200 c.c. in accordance with the age and size of the individual. The subdural space being chiefly potential, about one-half of this quantity is held in the subarachnoid clefts, and 20-30 c.c. in the ventricles. We have noted

¹ Jour. of Anat. and Physiol., 1892.

² Archiv für Anat. u. Physiol., 1890.

³ Davies, Jour. of the Acad. of Nat. Sciences, Philadelphia, 1869; also: Donaldson, The Growth of the Brain, 1895.

⁴ Studien über die Path. der Idioten, Upsala, 1895.

⁵ Jour. of Comp. Neurol., 1899.

⁶ First described by Haller, Physiol. des Menschen, 1766.

before that this subarachnoid space does not possess the same height throughout the encephalon, but shows cistern-like enlargements at different points, and especially over the corpus callosum and the optic lobes. Over the upper and lateral aspects of the brain it is very narrow. It has also been mentioned that it is traversed by numerous fibers and bands, so that it really becomes subdivided into a multitude of intercommunicating cells which in turn connect with the lateral ventricles, the central canal and subarachnoid space of the spinal cord, the lymphatic channels of the cranial and spinal nerves, and the

FIG. 360.—RIGHT LATERAL ASPECT OF THE SKULL AND CEREBRAL HEMISPHERE OUTLINED IN BLACK, WITH ORTHOGONAL PROJECTION OF THE STRUCTURES IN THE MEDIAN PLANE AND OF THE RIGHT LATERAL, THE THIRD AND THE FOURTH VENTRICLES IN RED. (Quain.)

Man aged fifty-six years. *a*, nasion; *b*, bregma; *c*, lambda; *d*, union; *t.r.*, temporal ridge; *s.c.*, sulcus centralis; *s.p.*, Sylvian point.

lymphatics of the nasal cavity and neck.¹ It seems, however, that the subdural and subarachnoid spaces are not directly connected with one another, although colored fluid injected into either cavity, eventually reaches the lymphatics of the nasal cavity as well as those of cranial nerves.

Cerebrospinal fluid may be obtained from animals by introducing a cannula through a slit in the sheath of a nerve root into the subarachnoid space of the spinal canal or by inserting it through the atlanto-occipital membrane into the cistern-like enlargement of the subarachnoid over the fourth ventricle. In man, it is now a rather common procedure to introduce a hollow needle directly into the spinal canal

¹ Walter, *Monatschrift für Psych. und Neurol.*, 1910, 28.

of the lumbar region, the needle being pushed inward between the laminae of the vertebrae. This constitutes the procedure of lumbar puncture¹ which is made necessary whenever small quantities of this fluid are to be obtained for chemical and histological analysis. Several cases are also on record, showing that a spontaneous discharge of cerebrospinal liquid may take place at times from the nasal cavity, averaging as much as 500 c.c. in 24 hours.

The fact that this fluid escapes from the cannula with some force shows that it is held under a certain pressure, equaling 5 to 7.3 mm. Hg. The flow decreases later on until only droplets appear. Various symptoms, such as vertigo, nausea and headache, result if it is allowed to drain off for too long a time. It is also of interest to note that the pressure of this fluid is about equal to that existing in the venous sinuses of the cranial cavity. Thus, if salt solution is injected into the subarachnoid space, it will be found to escape with relative ease, one of its channels of escape being the Pacchionian bodies. It seems, therefore, that these protrusions of the arachnoid membrane serve as filters, allowing a quick interchange of pressure between the cerebrospinal fluid and the blood in the sinuses. A similar interchange may be effected between this fluid and the lymph filling the lymphatics of the nerve roots, but the resistance interposed here seems to be much greater.

The cerebrospinal fluid is commonly regarded as a true secretory product (Mott) of the epithelial lining cells of the choroid plexus (Luschka). Others, however, consider it as a lymphatic fluid formed by transudation as well as by secretion (Lewandowsky). It cannot be doubted that this fluid possesses a certain independency, because biliary pigments frequently appear in the content of the subarachnoid space but not in that of the ventricles; and furthermore, the former often shows certain chemical characteristics which are not displayed by the latter.² It has also been found that its flow may be increased by extract of choroid plexus.³ Its formation, however, is slow under ordinary conditions, as has been shown by the experiments of Cavazzani,⁴ which prove that it takes about one hour before an easily recognizable salt injected into the general circulatory channels, may be detected in the subarachnoid fluid.⁵ In a similar way, it has been found that potassium iodid injected into the encephalic arachnoid cavity, appears in the urine only after about twenty minutes. In view of this close connection between the cerebrospinal fluid and the lymph, it seems best to consider the former as being derived from three sources, namely, (a) by secretion into the ventricle from the choroid plexus, (b)

¹ Quincke, Deutsche med. Wochenschrift, 1905.

² Thomson, The Cerebrospinal Fluid, New York, 1899.

³ Halliburton, Proc. R. Soc., London, 1916.

⁴ Centralbl. für Physiol., xiii, 14.

⁵ Plaut, Rehm and Schottmüller, Leitfaden zur Unters. der Zerebrospinalflüssigkeit, Jena, 1913.

by transudation into the subarachnoid and subdural spaces, and (c) by transfer from the intra-adventitial lymphatic spaces of the cortex.

Regarding its function it should be mentioned first of all that it serves the general purpose of lymph, because it bathes the nerve-cells. It forms a nutritive medium, which, in addition, is chemically protective, because it tends to exclude such harmful substances, as proteins and toxins. In the second place, it is mechanically protective, because it serves as a water-bed upon which rests the base of the middle and posterior parts of the encephalon, and which in other regions minimizes the force of blows upon the integument. In the third place, it may be conjectured that this fluid subjects the nervous tissue to a certain pressure which keeps it under a tension best adapted for its function.

Sleep.¹—Activity must always be followed by rest, because continued catabolic processes lead to fatigue and exhaustion. This holds true of the motor as well as of the sensory mechanism. A heart or skeletal muscle, when made to contract repeatedly, soon loses its irritability, because it is not allowed sufficient time to replenish the material lost during its periods of activity. This is also true of glands if made to secrete excessively, and of all sense-organs, if stimulated for a long period of time. What is true of individual tissues, is true of the body as a whole. It requires a period of recuperation during which its receptive power is at a minimum and during which it reestablishes proper physico-chemical conditions. Sleep is a universal phenomenon among animals; even the fish, reptiles and amphibians pass long periods of time in absolute quietude. The fundamental reason for sleep must, of course, be sought in chemico-physical changes, but our present knowledge of metabolism is not sufficiently advanced to explain the cause of this phenomenon in more than a very general manner.

While the daily requirement of sleep is about 7-8 hours for the adult, this time varies considerably under different conditions. In childhood, the amount of stored energy is small, owing to the immature development of the cells, while the metabolism, relatively rated, is intense, and hence, children require longer periods for recuperation. In old age, on the other hand, the small amount of stored energy is due rather to retrogressive changes and is associated with a lower metabolism, both factors combining to produce shorter hours of sleep. In either case, however, loss of sleep is injurious and even more so than the withholding of nourishment. Thus, Manaccine² has found that young dogs may withstand a starvation period lasting twenty days, but fail to recover from a loss of sleep extending over more than four or five days. These animals exhibited a fall in the body temperature of as much as 8° C. below normal, a diminution of the reflexes, fatty degeneration of diverse tissues, and hemorrhagic extravasations into the

¹ Piéron, *Le problème physiologique du sommeil*, Paris, 1913.

² *Contemp. Science Series*, London, 1897.

nervous tissue. Very similar changes have been observed in men deprived of sleep during a period of ninety hours.¹

The desire to sleep most commonly manifests itself by drowsiness, a general malaise, a heaviness and dryness of the eyelids, a difficulty in keeping the attention fixed, and other symptoms. This initial state soon gives way to a condition of unconsciousness during which the cortex is at least moderately impervious to external and internal stimuli. All volitional actions, therefore, cease, while the reflexes are in part preserved, although greatly diminished in their intensity. This shows that some parts of the central nervous system remain more active than others and this is true even of the cerebral cortex, because the motor center becomes inactive before the sensations have been lost entirely. Thus, a person may have reached the state of muscular flaccidity while still capable of receiving sensations of sound and touch.

The sense-organs themselves are in part protected against stimuli. The eyelids are closed and the eyeballs rolled far upward and inward. The pupils are markedly diminished in size. The latter effect may be explained in the same manner as the constriction resulting on near vision, *i.e.*, it may be said to find its cause in afferent stimuli set up in consequence of the convergence of the eyes. The conjunctival membrane becomes dry owing to a diminished secretion of lacrimal fluid, and is thus rendered less responsive to stimuli. A similar diminution in the sensitiveness is noted in the oral and nasal cavities. Their mucous lining also exhibits a certain dryness as a result of diminished secretion. The ears are protected by a relaxation of the conductors of sound situated in the middle ear, *i.e.*, the ear drum and ossicles.

Sleep having set in, the respirations become slower and deeper and are frequently accompanied by loud noises produced by the air as it rushes across the relaxed fauces, uvula, and edges of the laryngeal folds. In many cases the respirations assume a periodic character, a certain number of them being separated from others by a distinct interval of comparative rest. The frequency of the heart is greatly reduced; the vascular channels are relaxed and the blood pressure lessened. From these changes it may justly be inferred that the tissues have entered upon a state of relative inactivity; their low oxygen requirement and small output of carbon dioxide clearly betraying a decided reduction in their oxidations.

Changes in the Depth of Sleep.—Although sleep lasts as a rule for a certain number of hours, it does not retain the same depth throughout this period. This has been shown by endeavoring to awaken a person at different intervals by sounds of measured intensity. A pendulum beating against a metal plate, or small lead balls falling upon a metal surface, have usually been used for this purpose.² While individual variations are very common, the results show that the intensity of sleep increases steadily until it reaches its maximum

¹ Patrick and Gilbert, *Psychol. Review*, iii, 1896.

² Mönninghoff and Piesbergen, *Zeitschr. für Biologie*, xix, 1883.

between the first and second hours after its beginning. It then decreases and remains rather light during the third and fourth hours. A second but much slighter increase takes place during the fifth hour. From here on it again decreases up to the hour of awakening.

Theories of Sleep.—The theories pertaining to the causation of sleep, may be conveniently arranged as follows:

(a) *Anemia Theory* (Coppie, 1854).—It is held that the diminution and loss of the irritability of the cerebrum, and especially of its cortical zone, is dependent upon a decrease in its blood-supply. This view is based chiefly upon the experiments of Mosso¹ which have shown that the volume of the arms and legs increases during sleep, presumably on account of a transfer of blood from the cerebral into the cutaneous circulatory channels. This transfer may be effected in two ways, namely, by a constriction of the cerebral blood-vessels² or by a relaxation of the blood-vessels in other parts of the body. The extracerebral circuits which could be concerned in producing this diminution in the vascularity of the brain, are those of the integument and portal organs.

These facts have been made use of by Hill³ in formulating a theory which has as its chief element the fatigue of the vasomotor center. It is assumed that sleep results in consequence of the loss of tonus of this center brought on by the continued activity during the working hours. This loss of the vascular tonicity in turn leads to lower pressures and diminishes the blood flow throughout the body, but more particularly that through the brain. The blood withdrawn from the cerebral circuit, is said by Hill to be accommodated in the blood-vessels of the portal organs, while Howell believes that it is transferred into those of the skin and subcutaneous tissues. Brodmann⁴ and Shepard⁵ however, claim that the volume of the brain is increased, during sleep, as is also that of the limbs. This contradiction of the results of the investigators just cited, necessitates a certain modification of the anemia theory, because it places the transfer of blood from the brain into other blood-vessels into question. At best, therefore, we can go no further than to state that the vascular relaxation and depression resulting during sleep, is general and does not produce an actual anemic condition of the brain.

(b) *Inhibition theory*, advocated by Brown-Séquard,⁶ refers sleep to an inhibition of cortical function, such as may be produced by passing an induction current of low tension through the cranium (Leduc). This view has few points in its favor, because it does not attempt to explain the mechanism by means of which this inhibition is brought about.

(c) *The mechanical block theory* refers sleep to an interruption of the conduction paths caused by a retraction of the terminal fibers of the synapses.⁷ This view must also be said to contain a decided element of speculation, because it has never been demonstrated that a retraction of this kind actually takes place.

(d) *The chemical theories* of Preyer,⁸ Piéron⁹ and Pflüger¹⁰ refer the loss of the irritability of the brain to a fatigue brought on by chemical means. Thus, it has

¹ Ueber den Kreislauf des Blutes im menschl. Gehirn, Leipzig, 1881; also: Brush and Fayerweather, *Am. Jour. of Physiol.*, v, 1901, 199.

² Jenson, *Pflüger's Archiv*, ciii, 1903, 171.

³ *Physiol. and Pathol. of the Cerebral Circulation*, London, 1896, and Howell, *Jour. of Exp. Med.*, ii, 1897, 313.

⁴ *Jour. für Psych. und Neurologie*, i, 1902, 10.

⁵ *Am. Jour. of Physiol.*, xxiii, 1909.

⁶ *Archiv de physiol.*, 1889, 333.

⁷ Duval, *Compt. rend. de la Soc. biol.*, 1895; Cajal, *Archiv für Anat. und Physiol.*, 1895, and Nicard, *Le sommeil normal*, Lyon, 1904.

⁸ *Centralb. f. d. med. Wissensch.*, xiii, 1875.

⁹ *Le problème physiol. du sommeil*, Paris, 1913.

¹⁰ *Pflüger's Archiv*, x, 1875, 468.

been suggested that the constant activity of the muscles and other organs during the waking hours gives rise to waste products which accumulate in the system, because they cannot be gotten rid of as rapidly as they are produced. In the course of time, these substances cause a nervous depression which eventually culminates in sleep. While this theory also lacks experimental confirmation, it has certain points in its favor. Thus, it is a well-known fact that the activity of muscle is associated with the production of fatigue substances, such as carbon dioxid, sarcolactic acid and monopotassium phosphate. The accumulation of these substances in muscle finally causes the latter to lose its irritability. Furthermore, if the serum of a fatigued animal is injected into the circulatory channels of a normal animal, the latter will show all the phenomena of fatigue.

Some physiologists, among them Piéron, have gone a step farther and have stated that these fatigue substances are augmented by a special toxin which might be designated as a hypnotoxin. It is this agent which is assumed to produce the histological changes in the cells of the brain after forced deprivation of sleep. Its presence has been established by injecting the blood serum or cerebrospinal fluid of such animals into the circulatory channels of normal animals. The latter then showed a condition simulating sleep as well as structural changes in the cerebral cortex.

Pflüger explains sleep by assuming that the cells of the brain are quite unable to replace their store in intramolecular oxygen as rapidly as it is used up and hence, their irritability must decrease gradually with the length of the period of activity. This idea, however, that oxygen is stored in the cells as a product of a distinct synthesis is not commonly accepted to-day. The foregoing brief discussion must show that this subject is still in a very indefinite form, so that it might seem advisable to adhere for the present to the chemical theory and to consider the changes in the pressure, flow and distribution of the blood as secondary phenomena.

Hypnotic Sleep.—This condition is by no means identical with sleep. It is brought about by producing the picture of hypnosis by suggestion, a process which may be greatly facilitated by fixing the attention of the subject upon a constant visual, auditory or tactile stimulus, such as a glistening object, a monotonous sound, or slight stroking of the skin. Facilitation of this process is effected in time by repeated hypnoses until eventually a condition of autohypnosis may be induced, *i.e.*, an ability on the part of a person to self-induce this state (Cardanus, 1553).

Contrary to sleep, the hypnotized person exhibits a decided blanching of his features, a muscular relaxation, a drooping of his eyelids, slow and deep respirations and a peculiar change in his consciousness which is characterized by a decided vulnerability to suggestions. The vascular changes are betrayed by a decrease in the volume of the arms and legs, when determined by means of the phlethysmograph. Deep hypnosis, moreover, insures a loss of voluntary control of the muscles and certain sensory disturbances, such as amnesia, analgesia and anesthesia for touch and temperature. Curiously enough, this loss of the self-regulation of muscular movements does not include the control of the voluntary muscles through suggestion. Thus, it is possible to force a hypnotized person to assume different positions or to inhibit the action of his muscles, so that he cannot extricate himself from the most awkward idiomuscular situations. In fact, his muscles may be tonically set, so that the body becomes perfectly rigid and may

be subjected to most unusual conditions. Quite similarly, it is possible to influence his mental concepts in such a way that memories of certain past experiences are lost, while others are artificially created, thereby changing the entire character of the person. He may assume the character of a typical paralytic, blind or deaf person. Some of these suggestions may even produce posthypnotic results many days and weeks after the hypnosis. Thus, when a postage stamp was placed upon the skin of a hypnotic and it was suggested to him that it would raise a blister, such a formation was actually found beneath it on the following day. Subcutaneous hemorrhages may be induced in the same way, and so may "brand-marks" by simply suggesting to the hypnotic that, say, a piece of chalk used upon the skin, is a red hot iron.

Hypnotic states may also be evoked in animals. Thus, it is not difficult to render frogs, birds and rabbits motionless by a continued gentle pressure upon the dorsal aspect of their body, such as may be produced by holding them in the palm of the hand. A lobster may in this way be made to stand upon its head supported only by the first pair of appendages. Kircher's *experimentum mirabile* (1644) consists in rendering a fowl temporarily quiescent by placing a straw across its bill or by fixing its head in such a way that the eyes look directly at a chalk line drawn across the table. Verworn,¹ however, states that this is not an instance of true hypnosis but solely one of optical inhibition of reflexes.

Narcosis.—Omitting the largely speculative theories regarding the causation of narcosis, it has always been supposed that the narcotics enter into a chemical combination with the constituents of the protoplasm. In analogy to this union might be mentioned the action of curarin upon the motor nerve-endings or that of carbon monoxid upon the hemoglobin. Peculiarly enough, certain narcotics of the aliphatic series are chemically inactive, although capable of inducing a characteristic narcotic action. It was subsequently found that all possess the property of being dissolved in water and fats, this property being responsible for their absorption and distribution to the cells of the body. Bibra and Harless,² therefore, conceived the idea that the action of the anesthetics is dependent upon their power of dissolving fat. This hypothesis, however, seems untenable, because it fails to explain the rapid restitution of function following the anesthetization. In other words, it seems unlikely that the fat dissolved out of the nervous tissue to institute narcosis, can again be replenished in so short a time.

While no definite theory of narcosis has been formed to supplant the preceding, some interesting data have been gathered which partly explain the anesthesia. Thus, it has been shown by Meyer³ and

¹ Die sogenannte Hypnose der Tiere, Jena, 1898.

² Über die Wirkung des Schwefeläthers, 1847.

³ Archiv für Exp. Path. und Pharm., vi, 1901, 12.

Overton¹ that the narcosis depends upon the solubility of the narcotic agent in fats and oils. In general, those substances act as narcotics which are more readily soluble in fat-like media than in water; in fact, the power of these agents is directly proportional to their fat solubility. It has also been established that their action is produced by the free molecule and not by the products of their decomposition. Thus, the esters of the fatty acids narcotize only while they remain unsaponified. They lose this property as soon as they are split into the corresponding alcohol and fatty acid. This characteristic effect upon the nervous system is made possible by their going into solution with the fat-like constituents of this tissue, the lipoids. As nervous tissue contains an especially large amount of these substances, the narcotics must be capable of entering this tissue much more easily than others.

Having shown that the accumulation of the narcotics in the nervous tissue is due to their solution-affinity for the lipoids, we may go one step farther and state that the essential cause of narcotic action is the solution-reaction between them and the lipoids. In this connection, it might be mentioned that Höber² has found the colloidal state of the cells to be changed during narcosis, and that Winterstein³ has proved that narcotized tissue ceases to take up oxygen even when made to produce work in a superfluity of this gas. The evidence tends to show, however, that while the inhibition of oxidation constitutes a factor in narcosis, it is not actually its cause.

¹ Studien über die Narkose, Jena, 1901.

² Zeitschr. für allg. Physiol., xi, 1910, 173.

³ Ibid., vi, 1907, 315.

PART VI

THE SENSE-ORGANS

SECTION XX

SPECIAL SOMATIC AND VISCERAL RECEPTORS

CHAPTER LIX

CLASSIFICATION OF THE SENSE-ORGANS

The Different Manifestations of Energy.—Until now we have regarded the central nervous system as a mechanism controlling our various motor actions in a way to conform with the conditions existing in our environment. As such it occupies a position intermediate between the different afferent and efferent paths, fulfilling the function of a machine which converts or synthetizes the incoming impulses into motor responses. We have previously seen that the efferent side of this circuit is not greatly diversified, because all the effectors in our body are built up either of muscle-tissue or glandular tissue. On the afferent side, on the other hand, we find a decided multiplicity in structure to correspond with the diverse character of the influences to which we may be subjected.

Our body is surrounded by a medium which is teeming with manifestations of energy in its different forms. Against these the body is partially protected by a relatively impervious capsular investment, the skin. Here and there, however, this investment is beset with orifices for the admission of those stimuli which are essential to our life. These perforations really correspond to the windows of a house which enable us to come into functional relationship with the outside world. This is also true of the lower animals and even of those forms which are not in possession of a nervous system. In the latter, the different manifestations of energy are brought to bear directly upon their living substance, but not in an indiscriminate manner, because, with the exception of a few, these organisms are all at least partly protected against excessive stimuli by some sort of an enveloping membrane or calcareous shell. Furthermore, all these organisms possess a much more limited range of excitation than the higher forms, so that they are open to only a few types of stimuli, principally to those of mechanical and thermal origin.

Recurring to the analogy of the house with the many windows, it may then be said that these different openings are beset with a specialized form of protoplasm which, owing to its chemico-physical constitution, is especially sensitive to energy impressions from without, and is also modified in such a way that it can receive only one particular kind of stimulus. In other words, these sense-organs or receptors show individual differences which render them more particularly adapted to a certain type of energy manifestation. Thus, the retina of our eye cannot be activated by sound waves, nor can the organ of Corti be stimulated by the ethereal impacts of light. Each receptor, therefore, is set aside for only one kind of stimulus and remains impervious to others not specifically suited for it. It is true, however, that in most cases these receptors may be subjected to non-specific stimuli artificially, but the effects are then quite different from normal. Thus, it is possible to stimulate the retina either mechanically or electrically, in which case visual sensations in the form of phosphenes will be obtained, but these sensations are obviously very different from ordinary light impressions.

This specificity of the different sense-organs is to be attributed to the peculiar structure and composition of the neuroplasm forming them. Their function, however, is materially enhanced in many cases by the fact that the nervous terminals are amplified by certain accessory structures which tend to concentrate the stimuli precisely upon the receptor so as to intensify their force. Thus, we find that the essential receptive element of the eye is the retina, while the different refractive media of this organ, together with the iris, merely serve the purpose of concentrating the light rays upon its most sensitive constituent. The same is true of the organ of Corti, because the external ear, the eardrum, and ossicles merely serve to increase the striking force of the sound waves and to direct them to the sensitive epithelium in the cochlea.

The orifices in our integument in which the different sense-organs are placed, form, so to speak, points of least resistance through which the energy manifestations in space may reach the interior of our body. But, as has been stated above, each gateway permits of the entrance of only one particular kind of impact, because its resistance toward the others is heightened sufficiently to exclude them. In general, it may be said that we are subject to two types of energies, namely, the vibratory and the chemical, which in turn have been classified by Herriek¹ as follows:

A. Vibratory Energy.

1. *Mechanical impacts* received by the tactile corpuscles of the skin at a rate of as high as 1552 vibrations in a second.

2. *Slow vibrations in material media* received by the organ of Corti, and subjectively perceived as sound. The human ear is activated by vibrations varying between 30 and 30,000 in a second. In some cases, however, this range may be extended to 40,000 and 50,000 vibrations per second.

¹ An introduction to Neurology, Saunders Co., Philadelphia, 1915.

3. *Rapid vibrations in ether*, or waves in immaterial media, received by the temperature corpuscles of the skin (heat-rays) and the retinae of the eyes (light-rays). These vibrations, however, also include some to which we are absolutely insensitive or which can only be perceived with the help of certain accessory means. The Hertzian electrical waves attain a vibratory frequency of 3000 billions per second, the ultra-violet rays one of 5,100,000 billions per second, and the Roentgen-rays one of 6,000,000,000 billions per second. In between these two extremes lies the receptive scale of man. Thus, we find that our retina is capable of receiving impacts, the vibrations of which vary between about 400,000 and 800,000 billions per second. This range covers the solar spectrum. Between these vibrations and those attaining a frequency of 3000 billions per second, lies the realm of the radiant heat which stimulates the temperature receptors of our skin.

B. Chemical Energy.

The different chemical impacts to which we may be exposed, are received in a relatively imperfect manner. The organ of smell covers a much wider range than the organ of taste; in fact, the latter gives rise to only four fundamental sensations, namely, sweet, bitter, salty and sour.

Classification of the Sense-organs.—The foregoing discussion shows first of all that under ordinary conditions only a limited number of the energies developed in space, are made accessible to man. This statement, however, is not meant to imply that the equipment of other animals is as good as that of man; in fact, the chances are that it is not, for the reason that the human nervous system attains the most perfect all around development. It cannot be doubted, however, that the sensory mechanisms of a particular group of animals may be more fully developed along certain lines than those of others. This is especially true of the olfactory apparatus; but may also be true, for example, of the visual and auditory mechanisms of the birds as against those of man. At all events, provision has been made in each case to equip the different animals more especially with those sense-organs which are of greatest practical use to them.

Man has been placed in a position to analyze the energy manifestations in space by means of five senses, *i.e.*, he is able to bring five different means to bear upon the forces of nature for purposes of orientation. The sense-organs concerned in this analysis, are commonly said to be the eyes, ears, nose, tongue and skin. In agreement with this classification the layman recognizes five senses, namely, sight, hearing, smell, taste and touch. One discrepancy, however, must occur to us immediately, namely, that this classification does not embrace the large number of different receptors which are concerned with the reception of stimuli arising in the interior of our body. In the second place, attention should be called to the fact that several of the original five senses are really composite in type. Obviously, the ear contains not only the organ of hearing, but also separate receptors for the static and dynamic senses. Quite similarly, the skin is not only concerned with touch, but also mediates the sensations of pressure, pain, and temperature. To be brief, it will be brought out later on that there are in reality more than twenty different receptors in our body.¹

¹ Öhrwall, Skand. Archiv für Physiol., xi, 1901.

The preceding discussion must have shown that the central nervous system really performs two important functions, namely, to control the activities of the different tissues and organs, and secondly, to bring the latter into a proper relation with the outside world. Since this control is effected with the help of two different groups of nervous structures, the central nervous system may be divided theoretically into a visceral and a somatic part. For the same reason, the sense-organs may be classified as visceral and somatic, the former having to do with the sensations arising within our body, and the latter with those produced by the energies in space. It should be noted, however, that these groups of organs are not functionally isolated from one another, but are closely correlated so that they can always influence one another. Thus, we find that a visceral sensation may give rise to a somatic response, and *vice versa*. This classification has been made more embracing by Sherrington,¹ who divides the somatic group of receptors into exteroceptors and proprioceptors, and the visceral group into general and special interoceptors, as follows:

A. *Somatic receptors*, having to do with the orientation of the animal toward its environment.

1. *Exteroceptors*, are stimulated under ordinary conditions by outside forces. They embrace the end-organs for: (a) touch and pressure, (b) pain, (c) heat and cold, (d) general chemical sensibility, (e) hearing, and (f) vision.

2. *Proprioceptors*, are situated in the muscles, tendons and joints and are concerned with the production of the muscle-sense. To this group also belong the end-organs which have to do with the sensations of equilibrium, namely, the otolithic cavities (static sense) and the semicircular canals (dynamic sense).

B. *Visceral receptors*, are concerned with the stimulations arising within the body, principally in connection with digestion, secretion, the action of the heart, and other functions.

1. *General interoceptors*, embrace the end-organs, mediating the sensations of hunger, thirst, nausea, respiratory and circulatory sensations, sexual sensations, visceral pain, and others.

2. *Special interoceptors*, consist of the end-organs for taste and smell. Both are excited by chemical stimuli and while both are typical interoceptors to begin with, the organ of smell eventually becomes more closely associated with outside conditions.² In the amphibians and allied animals it is really the chief exteroceptor, although its more primitive interoceptive qualities are still in evidence.

Like the animals, plants are also exposed to varying conditions in the environment and are in possession of intensifying receiving organs. As such may be classified the bristles upon the leaf of *Dionæa* as well as those upon the stems and leaves of *Mimosa pudica*.

The Doctrine of the Specific Nerve Energies.—It is by no means difficult to see that the energy manifestations give rise to very specific sensations and reactions. The question then arises, whether this specificity is due to peculiarities in the energy or to peculiarities in the structure of the sense-organs. Johannes von Müller favors the second view without, however, positively referring it to any particular segment of the neuron. In more recent years physiologists have gone a step

¹ The Integrative Action of the Nervous System, New York, 1906.

² C. J. Herrick, Jour. Comp. Neurol., xciii, 1908, 157.

farther and have rather generally concluded that the specific quality of a sensation in consciousness is dependent upon the center and not upon the conducting path nor upon its receiving organ. The second possibility may, of course, be justly ruled out, because nerve fibers are conductile elements and nothing more than that. The third possibility cannot be excluded so easily, because the sense-organs exhibit particular structural details which render them especially adapted for the reception of single kinds of energy manifestations. On the other hand, it is evident that this specificity of the end-organ could not be of any avail, were it not for the fact that the center possesses a similar specificity. Besides, since the latter is commonly regarded as the controlling factor of all nervous processes, it may also be considered as the determining agent of these impressions in consciousness. Consequently, the end-organ merely enables a particular stimulus to enter, and determines whether or no the latter should become effective centrally. Thus, if it were possible to cross the optic and auditory nerves, so as to connect the retina with the auditory center and the organ of Corti with the visual center, we would hear pictures and see sounds.

The experimental evidence which might be mentioned in favor of the doctrine of specific nerve energy, includes such positive data as the following:

(a) An impression in consciousness is often obtained without the help of the sense-organ and conducting path. For example, subjective sensations of light are frequently gotten in a perfectly dark room and when the eyes are closed. Ringing in the ears is another common subjective phenomenon. Central causes must also be held responsible for the multitude of concepts obtained during dreams and in consequence of pathological conditions, such as arise during hysteria and states of excessive sensitiveness of the nervous system.

(b) The different sense-organs may also be activated by stimuli other than those ordinarily received by them. Thus, sensations of light may also be produced by exerting a slight pressure upon the eyeball or by passing an electrical current through it. Quite similarly, an electrical current directed through the tongue, evokes sensations of taste, but sensations of touch, when applied to the skin. A tuning fork made to vibrate in the vicinity of the ears, gives rise to sound sensations, and when allowed to beat against the skin, to the peculiar tactile impression known as tickling.

(c) Very similar effects may be obtained by the stimulation of the nerve fibers leading away from these sense-organs. Thus, the cutting of the optic nerve evokes flashes of light, while the excitation of the chorda tympani during its course through the tympanic cavity gives rise to sensations of taste upon the tip of the tongue. In many cases, these diverse sensations are elicited in consequence of tumors, exudations, and hyperemic conditions in the course of sensory nerves.

(d) Sensations may be dissociated. A degree of pressure may be brought to bear upon the skin which destroys the sensation of touch and temperature, but not that of pain. This preservation of one particular cutaneous impression to the exclusion of others, is frequently observed in the beginning stages of degeneration and regeneration following the division of peripheral nerves. This dissociation may also be effected by chemical means, for example, the taste of bitter may be destroyed by cocain and that of sweet by gymnemna sylvestris.

The Modality of a Sensation.—It is a matter of common experience that the different sensory impressions are not referred to the brain at

all, but are projected to the sense-organ in which they have arisen and even beyond the latter to the area in space from which they have been derived. Thus, the sensations of touch are referred to the surface of the body and those of taste to the tongue and mouth. Quite similarly, the sensations of sight and hearing are always interpreted as having been received from a particular realm in space. It must be evident, therefore, that a sensation cannot be regarded as a definite cortical concept, because since judgment enters this act, which always comprises other activities, the resultant impression is really the symbolical picture of the conditions mediated from without.

Each sensation, however, is symbolized independently of the others, because the sensations of light are distinct from those of taste, smell, hearing and touch. This implies that every one of them possesses a definite quality or modality which we have learned to recognize in the course of time. In spite of this fact, however, it would be quite impossible for us to compare these modalities with one another. To be sure, we clearly understand what is meant by the sensations of bitter, an intense light, a low pitched sound, and other impressions, although we are unable to estimate the precise character of these qualities so as to be able to say, for example, that this sound is louder than this taste is sweet. Consequently, each sensation possesses a modality which is absolutely specific to it. Sensations mediated by one and the same sense-organ, however, we are able to rate in a quantitative manner, because we clearly recognize differences in the pitch of the sounds and in the intensity of the light, and are able to tell that the sweet taste of a given substance is more pronounced than that of another.

Fatigue and Adaptation.—While the different receptors may be activated by stimuli of a non-specific character, they are usually open to those kinds of impacts only for which they are especially constructed. It may be said, therefore, that the sense-organs form channels of least resistance through which appropriate stimuli are allowed to pass with the least possible loss of energy to them. Beginning with this minimal or threshold value, an increased strength of stimulation always gives rise to a more intense sensation, but an upper limit is finally reached beyond which a further augmentation is impossible. This augmentation, however, is not always proportional to the intensity of the stimulus, because an undue strength or duration of the stimulation invariably results in a fatigue which seems to affect primarily the recipient centers. It is also evident that the sense-organs are much more receptive toward repeated stimuli of minimal strength than toward single stimuli of maximal strength. In addition, they possess the power of adaptation, which in many cases may be employed to intensify the primary sensation. Thus, we speak of a dark-adapted eye, *i.e.*, an eye which is at first kept in complete darkness so that it may later on be activated by much lower intensities of light than are ordinarily required to stimulate one which has just been exposed to light.

Weber's Law.—While it is true that the intensity of a sensation increases with the strength of the stimulus, the former does not preserve a direct relationship to the latter. Clearly, the different sense-organs are adjusted in such a way that they can receive their specific stimuli with the greatest possible ease; in other words, their threshold value is low. This implies that the maximum value of a sensation is attained very quickly and that stimuli of greater intensity do not augment the primary impression in any appreciable measure; in fact, their tendency is to produce fatigue. Now, while it is a relatively simple matter to determine the strength of the stimulus which is required to evoke a certain sensation, it is difficult to obtain comparative values of sensations, whether of the same or of different character. This inability on our part of rating sensations in an absolute quantitative manner forces us to rely solely upon our power of perceiving slight differences in them. One way of doing this is to ascertain how greatly a stimulus must be increased in order to give rise to an appreciable sensation of difference. Consequently, the only two means at our disposal for rating sensations in a quantitative way are first, the determination of the threshold value of the stimulus required to elicit a certain sensation, and secondly, the determination of the increase in the strength of the stimulus necessary to produce a distinct difference in the sensation.

E. H. Weber,¹ who first attempted to obtain such values, made the observation that the stimulus necessary to cause a sensation of difference, is proportional to the intensity of the stimulus then acting, *i.e.*, it forms a fractional increment of the latter. Subsequent determinations, however, have shown that this law holds true only for stimuli of moderate intensity. Thus, if a weight of 30 grams is placed upon the tip of the index finger of a hand supported at the wrist, and is properly adjudged by means of the muscle-sense, an additional weight of 1 gram must be added to or subtracted from these original 30 grams before a distinct difference in this sensation will be obtained. If this test is now repeated with a primary weight of 60 grams, it will be found that 2 grams are required in order to produce a sensation of difference, and with 90 grams an additional weight of 3 grams, and so on, until the physiological limit is reached at about 1000 grams. In this particular case, therefore, the increment is $\frac{1}{30}$ of the original stimulus. Naturally, this law holds true for any quality of stimulus, provided that the latter is of moderate intensity. For sounds the appreciation difference is $\frac{1}{9}$, and for light $\frac{1}{120}$ of the original stimulus. Consequently, the eye is the most sensitive organ.

Fechner's Psychophysical Law.—The attempt has been made by Fechner² to generalize the preceding law and to place it upon an accurate quantitative basis. It is stated that the sensations show the same relationship to the stimuli as the logarithms to their numerals. Fechner's law, therefore, may be expressed by the formula $S = C$

¹ Wagner's Handwörterbuch der Physiol., iii, 1846, 481.

² Elemente der Psychophysik, Leipzig, 1860.

log R , in which S indicates the sensation, R the stimulus and C the constant represented by the difference in the sensation. But this conception, that the sensation is proportional to the logarithm of the stimulus, must meet with serious objections, because it has been proved that Weber's law is not applicable to stimuli of low and high intensity. In addition, Fechner has assumed that the smallest appreciable increase in the sensation must always remain the same, *i.e.*, the difference in the sensation obtained when 1 gram is added to 30 grams, must be the same as that evoked by the addition of 2 grams to 60 grams. Physiological observation has proved this assumption to be incorrect, and hence, we may justly advocate the view of James, that the attempt to measure sensations with mathematical precision, is a mere speculation.

CHAPTER LX

THE SENSES OF PRESSURE OR TOUCH, PAIN, AND TEMPERATURE

The Structure of Cutaneous Receptors.—The integument of our body is permeated by two sets of nerve-plexuses, one of which is situated in the panniculus adiposus and the other in the stratum subpapillare. Both ramifications give rise to fibrils which terminate in peculiar end-organs in almost all layers of the skin. The most common of these consist of medullated fibers from the dermal plexus which give off branches and soon lose their medullary sheath. The latter pierce the epidermis and then form arborizations among the cells of the Malpighian layer. The different fibers end bluntly or are expanded into distinct sensory plates. Phylogenetically considered the latter formation is the more recent.

FIG. 361.—TACTILE CORPUSCLE WITHIN A PAPILLA OF THE SKIN OF THE HAND, STAINED WITH CHLORID OF GOLD. (Ranvier.)

n, Two nerve-fibers passing to the corpuscle; *a*, *a*, varicose ramifications of the axis-cylinders within the corpuscle.

bodies which attain a length of from 2–4.5 mm. and a breadth of 1–2 mm. Their outer zone consists of concentric lamellæ, while their core is penetrated by a nerve

The corpuscles of Meissner (1852) are found in the papillary and subpapillary layers of the skin. They acquire a length of from 40–100 μ and exhibit an oval or round-elliptical outline. Their outer zone consists of connective tissue lamellæ which invest a core of reticular tissue through which one, two, or several non-medullated nerve fibers wind their way spirally to the tip of this structure. A very similar arrangement is presented by the Golgi-Mazzoni corpuscle (1880) as well as by that described by Vater and Paccini (1840). The latter are small oval

fiber which may be single or split up into a delicate ramification. These end-organs are very numerous in the subcutaneous connective tissue. The corpuscle of Herbst which is chiefly found in birds, is somewhat smaller, but very similar in structure to the preceding. Another cutaneous receptor has been described by Krause (1860). It is globular in shape and its central region is taken up by the arborization of the nerve fiber. Equally characteristic and suggestive of their function are the corpuscles of Grandry and Merkel. They consist of two or several hemispherical cells with flattened surfaces, between which the nerve fiber is expanded. Their height measures 15μ and their breadth 50μ . The composite type of these corpuscles is present in great numbers in the skin of the bill and tongue of birds. Several different types of endings have been found around and in the immediate vicinity of the roots of hairs.

FIG. 362.—PACCINIAN CORPUSCLES FROM THE PERITONEUM OF A CAT. (After Sala, from Böhm-Davidoff-Huber's *Histology*.)

Methods Used to Evoke Tactile Sensations.—The skin is exposed to influences which are capable of eliciting several kinds of sensations, namely, pressure, touch, pain, cold, warmth, tickling, and others of a more composite type. The sensations of pressure and touch are dependent upon mechanical stimuli and find their origin in a displacement of the surface layers of the skin.¹ They represent sensations caused by different grades of the same mechanical impact, but the displacement need not take place in an inward direction but may also result in consequence of pull upon the surface. In the former case we obtain a positive and in the latter a negative imprint.

The tactile sensations are usually tested by means of an instrument, which is known as an esthesiometer. In its simplest form it consists of a hair or fiber of glass-wool attached to a handle, the tip of which

¹ Frey and Kiesow, *Zeitschr. für Psych. und Physiol. der Sinnesorgane*, xx, 1899.

is pressed upon the skin with a force sufficient to elicit different intensities of tactile impressions. This method permits of the determination of the acuity of these sensations as well as of our ability to localize them with accuracy. Esthesiometers are also in use which possess two points of contact adjusted at varying distances from one another. This arrangement allows us to determine how far these points must be separated from one another in order to give rise to two distinct sensations. Our ability to tell whether a tactile stimulus is single or double, is known as tactile discrimination.

FIG. 363.—HERBST CORPUSCLES OF DUCK.

n, Medullated nerve-fibre; *a*, its axis-cylinder, terminating in an enlargement at end of core; *c*, nuclei of cells of core; *t*, nuclei of cells of outer tunica; *t'*, inner tunica (*Sobotta*) $\times 380$ diameters.

Tactile Acuity, Localization and Discrimination.—We have seen that the adequate stimulus for sensations of touch is a mechanical impact which causes a deformity of the surface of the skin and thus activates the sensory nerve-endings contained therein. This activation, however, is accomplished under normal condition with the help of certain adjuncts consisting in peculiar capsular investments of the terminals of the sensory nerve

fiber. Thus, we find that the threshold value of a stimulus applied to the tactile capsule, is very much lower than that required to

FIG. 364.—KRAUSE'S CORPUSCLE. *A* AND *B*, GENITAL CORPUSCLES FROM THE CLITORIS OF THE RABBIT (*Izquierdo*); *C*, FROM THE HUMAN CLITORIS. (*W. Krause*.)

elicit a sensation from the nerve fiber itself. It is evident, therefore, that the skin is in possession of what might be termed tactile

points, but experimentation has shown that these points are not evenly distributed throughout the skin, but are more numerous and

FIG. 365.

FIG. 365.—CORPUSCLES OF GRANDRY FROM THE DUCK'S TONGUE. (*Izquierdo.*)

A, compound of three cells, with two interposed discs, into which the axis-cylinder of the nerve, *n*, is observed to pass; in *B* there is but one tactile disc enclosed between two tactile cells.

FIG. 366.

FIG. 366.—GRANDRY CORPUSCLE IN TRANSVERSE SECTION. (*After Dogiel.*)

more sensitive in some regions of the integument than in others.

FIG. 367.—SENSORY NERVE TERMINATING IN ARBORIZATIONS AROUND THE ENDS OF MUSCLE-FIBERS. (*Ceccherelli.*)

Their total number has been estimated at 500,000, excluding the region of the head. Upon the back of the leg, 1.0 sq. cm. of the skin

is said to contain about 15 of these tactile receptors.¹ The succeeding table shows how great a pressure must be brought to bear upon different regions of the skin in order to evoke minimal sensations; the degree of pressure being indicated here in grams per square millimeter of area:

FIG. 368.—COLD AND HOT SPOTS FROM THE ANTERIOR SURFACE OF THE FOREARM.

a, Cold spots. *b*, Hot spots. The dark parts are the most sensitive, the hatched the medium, the dotted the feebly, and the vacant spaces the non-sensitive. (*Landois and Stirling.*)

Tongue and nose.....	2
Lips.....	2.5
Finger-tip and forehead.....	3
Back of the finger.....	5
Palm of the hand, arm and thigh.....	7
Forearm.....	8
Back of the hand.....	12
Back of the leg and shoulder.....	16
Abdomen.....	26
Sole of the foot.....	28
Back of the forearm.....	33
Gluteal region.....	48

The acuity of the discriminating sense also varies in different regions of the skin, as may be gathered from the succeeding table:

Tip of tongue.....	1.1 mm.
Palm of the last phalanx of the finger.....	2.2 mm.
Palm of the second phalanx of the finger.....	4.4 mm.
Tip of the nose.....	6.6 mm.
Back of the second phalanx.....	11.1 mm.
Back of the hand.....	29.8 mm.
Forearm.....	39.6 mm.
Sternum.....	44.0 mm.
Region along spine.....	54.0 mm.
Middle of the back.....	67.0 mm.

¹ Vitreg, Ber. der sächs. Gesellsch. der Wissensch., xxiii, 1896, and Kiesow, Wundt's phil. Studien, xix, 1902.

It will be seen that the tongue, tips of the fingers and nose are the most sensitive regions. Other areas are frequently beset with hairs which tend to increase the intensity of the excitation in a perfectly mechanical way, because they act as levers upon the tactile corpuscles lying in the immediate vicinity of their roots. Moreover, the pressing down of their shafts tends to augment the displacement of the surface layers. Hairs, therefore, tend to lower the threshold value of the excitation and to impart to the latter a peculiar quality which renders stroking movements and all laterally applied impacts especially effective. Variations in tactile acuity may be produced by increasing or decreasing the blood-supply, by the administration of such drugs as morphin, strychnin and alcohol, and by training. Thus, we find that the tactile sense is especially keen in blind persons and in type-setters.

Touch Illusions.—Weber conceived the skin as being subdivided into a number of touch circles or, as Hermann has called them, touch areas, within the boundaries of which the two points of an esthesiometer are perceived as one. The size of these fields differs, a fact which may readily be deduced from the preceding table. It was assumed further that every one of these touch points is represented in consciousness by a local sign or quality which, however, does not retain a local character but is projected outward to the area of the skin stimulated. Furthermore, this sensation is not perceived as a rule in the form of a simple deformation of the surface of the skin, but as an actual reproduction of the object. In many instances, this projection is even extended to a point beyond the skin. Thus, we find that the peculiar grating sensation produced when cutting into bone, is not referred to the fingers, but to the knife itself.

Our associations pertaining to tactile sensations, may easily be upset by subjecting them to unusual conditions. This fact is typically illustrated by an experiment first described by Aristotle.¹ If the index and middle fingers of the right hand are crossed, a marble rolled around between their tips in the palm of the left hand will appear as two. This illusion is due to the fact that the crossing of the fingers brings two sets of tactile corpuscles together which are ordinarily far removed from one another and are rarely called upon to act in unison. Consequently, the corpuscles upon the radial side of the index finger, as well as those upon the ulnar side of the middle finger, give rise to separate sensations. Quite similarly, it has been observed that the tactile sensations obtained from a flap of the skin of the forehead which has been turned downward to cover a defect of the nose, are at first referred to the forehead. Later on, however, new judgments are formed, which enable the individual finally to localize these sensations correctly. If the tip of the nose is palpated between the tips of two crossed fingers, it appears as two.

¹Metaphysics, iii, Chapter 6.

The Sense of Pain.—Uncomfortable and painful sensations may be mediated by any sense-organ and even if the intensity of the stimulus is slight. This is true particularly of obnoxious odors, noises, very loud sounds and high intensities of light. As commonly interpreted, however, the word pain refers to a very definite sense quality which allows of a rather precise localization, while the painful sensations just alluded to, are indefinite and general in their character. Pain is widely distributed throughout the body, and is a common phenomenon even in the deeper tissues and organs. The most sensitive part, however, is the skin, as may be gathered from the fact that an incision in the integument always elicits a more intense pain than the handling and cutting of the deeper structures. According to Von Frey,¹ more than one hundred pain points are allotted to each 1 sq. mm. of skin. It also appears that the visceral receptors for pain cannot be activated by ordinary mechanical means. Thus, it is possible to operate upon the stomach and intestine without causing an acute sensation of pain, while inflammatory reactions in these organs or their distention by gases and subsequent spasmodic contraction give rise to intense gastralgia and colic. Quite similarly, it is commonly noted that the passage of biliary calculi through the common duct or of renal calculi through the ureters, evokes an intense pain in otherwise practically insensitive structures. In all these cases, it appears that the adequate stimulus is distention, pain resulting only if the degree of the distention exceeds that ordinarily required to obtain the sensation of physiological fullness.

As far as the cutaneous sensation of pain is concerned, it may be held that it is caused either by an overstimulation of the receptors for pressure and touch or by the excitation of specific sense-organs for pain. The second view is more commonly accepted to-day,² because the sense of pain possesses a punctiform distribution and is mediated by end-organs which yield solely this particular sensation. Thus, while the hyperexcitation of the touch points may give rise to an unpleasant sensation, the quality of the latter is distinctly different from that of true pain.³ In addition, it might be mentioned that the tactile and temperature senses may be absent in certain regions of the body, but not the pain sense. Thus, while the stimulation of the cornea readily elicits a painful sensation, it does not give a distinct sensation of touch. Furthermore, it is a common observation that pathological processes may give rise to an analgesia or loss of the pain sense, but not to an anesthesia or loss of the sense of touch.

Assuming, therefore, the separate existence of pain points, it seems most plausible to refer this sensation to the free endings of the nerve

¹ Arbeiten aus dem physiol. Inst. zu Leipzig, 1896.

² Brown-Séquard, Jour. de physiologie, vi, 1864, and Funcke, Hermann's Handb. der Physiol., iii, 1883.

³ Blix, Zeitschr. für Biol., xx and xxi, 1884-85.

fibers.¹ These sense-organs possess a high threshold value, *i.e.*, they remain insensitive until a certain upper limit has been reached when their excitation suddenly evokes pain. It is also evident that the latent period elapsing between their stimulation and the sensation, is unusually long; moreover, the quality of this sensation may be materially varied by the simultaneous excitation of other cutaneous receptors. For example, a burning pain results whenever the nerve-endings for pain and heat are activated together and a throbbing pain, whenever the receptors for pain and touch are jointly involved. A peculiar alternating character is imparted to the latter sensation by the systolic distention of the blood-vessels, and especially if it meets the resistance of hyperemic and infiltrated tissues. In this group of the composite sensations of pain also belong itching and tickling. Alrutz,² however, considers these impressions as being evoked by special nerve-endings, which implies that they represent two varieties of one and the same modality of sensation.

The pain sense forms an important protective mechanism of the body, because it acts as a danger-signal, by means of which abnormal processes may be detected. In many cases, it compels rest and thereby favors the healing of a diseased part. It should also be noted that a certain tissue may become painful by sympathy, *i.e.*, it may develop a decided tenderness in consequence of a diseased condition existing elsewhere. Diseases of the heart or aorta are sometimes associated with pain between the shoulders or with pain radiating outward into the arms. Referred sensations of pain are also experienced in inflammatory conditions of the appendix, gall-bladder and biliary ducts. Head³ has shown that the innervation of certain areas of the skin is intimately related to that of certain internal organs, because any particular segment of the spinal cord sends out an autonomic supply of nerve fibers as well as one to the corresponding region of the integument. In certain lesions of the central nervous system, the tactile sensations are sometimes wrongly referred to regions of the body which are actually far removed from those in which they have arisen. Most commonly, however, the corresponding area on the opposite side is believed to be the seat of the excitation. This faulty localization is designated as *allochiria* and constitutes a frequent tabetic symptom.

The Temperature Sense.—Contrary to the view that the sensations of heat and cold arise in consequence of the excitation of one and the same end-organ, it is now commonly believed that they represent two distinct modalities which are mediated by separate receptors. Thus, if a pencil-like probe through which warm water is made to circulate, is slowly drawn across the surface of the skin, a very decided sensation of heat is generally obtained in one place and none at all

¹ Thunberg, Nagel's Handb. der Physiol., iii, 1905.

² Skand. Archiv für Physiol., xvii, 1905.

³ Brain, xvi, 1893.

in the area immediately adjoining. Quite similarly, the mapping out of the surface with a thermæsthesiometer through which cool water is made to flow, yields sensations of cold within fields of no thermal stimulation. It appears, therefore, that the integument embraces a series of warm and cold points which when properly marked in different colors, will be seen to occupy dissimilar areas. The cold spots are more numerous than the warm spots, their relationship being as 13 : 1.5. In between these positive fields we have areas which do not give rise to a distinct temperature sensation and are, therefore, called indifferent fields. But these temperature points are not confined to the skin alone but are also disseminated through the mucous membranes of the mouth, nose, external auditory meatus, and anus.¹

FIG. 369.—HEAT AND COLD SPOTS ON PART OF PALM OF RIGHT HAND.

The sensitive points are shaded, the black being more sensitive than the lined, and these more sensitive than the dotted parts. The unshaded areas correspond to those areas in which no special sensation was evoked. (*Goldscheider.*)

The acuteness of the temperature sense varies in different regions of the body. Thus, it has been observed that the areas situated in the midline of the trunk, are less sensitive than those situated more laterally, and that the left side, in general, is more sensitive than the right.² The lateral aspects of the extremities are relatively insensitive. The same holds true of the mucous surfaces, when compared with the skin. Inasmuch as the latent period is shortest in the case of the cold points, the stimulation of a certain area of the integument most generally elicits the sensation of cold before that of heat. Moreover, the former sensation develops more rapidly than the latter and seems, therefore, to be the more intense. Much depends, of course, upon the size of the area stimulated. Thus, a finger immersed in water of a certain temperature always gives a more moderate sensation than the entire hand.

Von Frey believes that the sensation of cold is mediated by the corpuscles of Krause. The activation of these endings may also be

¹ *Zeitschr. für Biol.*, xx, 1884, 141; also Goldscheider, *Über den Schmerz*, Berlin, 1894, and *Gesellsch. Abhandlungen*, Leipzig, 1898.

² E. H. Weber, *Wagner's Handwörterbuch der Physiol.*, iii, 544.

effected by pressure or by the electrical current, a fact which is frequently cited in proof of the law of the specificity of nerve energy. Under ordinary conditions, these receptors are exposed to a constant temperature by reason of the steady stream of heat which escapes from the blood and permeates the tissues. The escape of this heat may be retarded by warm and increased by cold applications. Consequently, these thermal stimulations can only arise if the heat stagnation or dissipation surpasses the physiological minimum. This fact explains the sensation of cold, experienced whenever the circulation of a part is impeded or when especially good conductors of heat are applied to the body-surface. Since a more rapid fall in temperature is effected by the latter procedure, the nerve-terminals for cold are more quickly reduced below the point of minimal thermal stimulation. In other words, the chief factor in the production of the sensations of heat and cold is the temperature of the nerve-terminals mediating these senses.¹

Rather difficult to explain are the so-called paradoxical temperature reactions. Menthol applied to the skin, gives rise to a sensation of cold, while carbon dioxid elicits a sensation of warmth. A sensation of cold may also be evoked by stimulating a cold spot with an object possessing a temperature of 45–50° C. Very peculiar sensations of contrast arise in consequence of the adaptation of these sense-organs to certain temperatures. If the index finger of one hand is placed in water of 10° C., the primary sensation of cold eventually gives way to one of indifference. If this finger is then quickly transferred into water of 11° C., a distinct sensation of warmth will be obtained. Quite similarly, a sensation of cold may be evoked by transferring the finger from water of 39° C. into water of 38° C. Furthermore, having adapted the fingers of one hand to water of 35° C., and those of the other to water of 25° C., their simultaneous transfer into water of 30° C. produces a sensation of cold in the former and a sensation of warmth in the latter. If a warm coin is applied to the skin for some time, its removal gives rise to a sensation of cold, and even when the temperature of the surrounding medium is only very slightly below that of the skin.

CHAPTER LXI

THE SENSES OF SMELL, TASTE, HUNGER AND THIRST

A. SPECIAL INTEROCEPTORS. SMELL AND TASTE

The Structure of the Olfactory Organ.—The mucous membrane of the nose consists of ciliated reticular cells which are augmented, in the so-called olfactory area, by cells possessing all the characteristics of

¹ Hering, Sitzungsber., Akad. zu Wien, lxxv, 1877, 101.

receiving elements. This particular area occupies the nasal septum and adjoining region of the superior turbinated bone, and measures about 250 sq. mm. on each side. It is sharply differentiated from the general lining membrane of this cavity by its yellowish brown color.

Each nasal cavity may be divided into two regions, namely, into the so-called regio respiratoria and regio olfactoria. The former occupies the space between its floor, its median septum and the inferior and middle turbinated bones. It receives its sensory nerve supply chiefly from the second ramus of the fifth cranial nerve or trigeminus, while its upper part is innervated by the first branch of this nerve.

FIG. 370.—CELLS OF THE OLFACTORY REGION.

a, olfactory cells; *b*, epithelial cells; *n*, central process prolonged as an olfactory nerve fibril; *l*, nucleus; *c*, knob-like clear termination of peripheral process; *h*, olfactory hairs. (After v. Brunn.)

These fibers end free among the lining cells and mediate general sensations, namely, those of touch, pain and temperature. As such they may also be stimulated by irritating emanations, such as are derived from ammonia and acetic acid. In this region are also found numerous mucous glands, while those in the upper part of the nose are tubular.

The olfactory regions proper consist of non-ciliated columnar cells which are intermingled with a large number of modified epithelial cells.¹ The free ends of these slender nerve cells are beset with six to eight hair-like projections which extend through the limiting membrane into the lumen of the nasal cavity. Their basal portions are directly continuous with the fibers of the olfactory nerve, which pass through the pores in the cribriform plate of the ethmoid bone and eventually terminate in the olfactory bulb. They end here in arborizations in the olfactory glomeruli. Their further course has been mapped out in one of the preceding chapters.

In the lowest vertebrates the olfactory organ appears in the form of a rounded or long drawn out depression, which is connected with the olfactory nerve. In the selachia, these grooves are connected with the cavity of the mouth by a gutter-like prolongation. In the frog, this connecting passage is distinctly tubular. The cephalopods are in possession of ciliated olfactory pockets which are situated behind the eyes, while those of the arthropods are located upon the antennæ.

The Specific Action of the Olfactory Cells.—The respiratory currents of air traverse chiefly the lowest part of the nasal cavity, while the air in its upper region remains practically stationary. From this it

¹ Found in the frog by Eckardt in 1855, and in mammals by Ecker in 1856. M. Schultze gave an adequate description of these cells in 1863.

may be inferred that the odoriferous particles reach the olfactory area by diffusion. Their passage upward, however, may be greatly facilitated by the act of sniffing which tends to displace the air in the vicinity of the olfactory cells by air drawn upward through the fore part of this cavity. This act is, of course, inspiratory in its character, but it cannot be denied that the aforesaid cells may also be activated by the odoriferous particles derived from food and diverted into the nasal cavity by the expiratory air. The senses of smell and taste frequently act together, supplementing one another. In fact, it frequently happens that we project a sensation to the mouth which has actually arisen in the olfactory cells. The preceding data also serve to explain the long latent period usually intervening between the entrance of the odors into the nostrils and the sensation, the largest part of this period being required for the diffusion of the particles to the olfactory area.

Regarding the manner in which the olfactory cells are stimulated, little is known. It is evident, however, that the odorous substances emit particles which in most part are in gaseous form. Having arrived in the vicinity of the olfactory area, they enter into solution with the fluid bathing the lining membrane and eventually with the olfactory cells themselves. But only those bodies are capable of acting upon these cells which contain a chemical binder, the so-called odoriphore group, which possesses a chemical constitution, enabling it to unite with the substance of the olfactory epithelium.¹ Hence, smell is essentially a chemical process, consisting in an interaction between the activating body and the protoplasm of the olfactory cells. It is difficult to show this fact, because it is practically impossible to fill our nasal cavity completely with a fluid which is non-irritating. Aronsohn,² however, claims to have succeeded in evoking sensations of smell by means of isotonic solutions of sodium chlorid to which odoriferous substances had been added. In support of this chemical theory it might be mentioned that the aquatic animals are in possession of a projected chemical sense of smell which, in the nature of things, can only be evoked by substances held in solution.

The Power of Reaction of the Olfactory Cells.—Olfactometry.—

While the sensations of smell may also be evoked by stimulating the olfactory area with an electrical current, the adequate stimulus is, of course, the odorous molecule. Zwaardemaker³ has attempted to determine the stimulating quantity of different odoriferous substances by means of an instrument, known as the olfactometer. It consists as a rule of two tubes which are curved at their ends so as to facilitate their introduction into the upper part of the nasal passage. The free ends of these tubes are surrounded by somewhat larger tubes (6 mm. in diameter) which are imbibed with some odorous material. Naturally, the farther the outer tubes are shoved over the inner, the

¹ Haycraft, Brain, 1888, 166; also Pussy, Compt. rendus, 1892.

² Archiv für Anat. und Physiol., 1886.

³ Die Physiologie des Geruchs, Leipzig, 1895.

smaller will be the surface capable of sending odoriferous particles into the air inspired through this tube. This method enables the experimenter accurately to grade the stimulating quantity.

The amount of substance necessary to excite the olfactory mechanism, is extremely small. Thus, 0.01 mg. of mercaptan may be perceived if diffused through 230 c. cm. of air, so that each liter of the latter contains only 0,000,000,04 mg. of this substance.¹ The threshold value of ether and oil of wintergreen is 0.0005 mg. per liter of air. Camphor stimulates in a dilution of 1 part to 400,000, musk in the proportion of 1:8,000,000 and vanilla in the proportion of 1:10,000,000. The acuity of the sense of smell differs in different persons, and is subject to various exherent factors. It is said that women, and especially children, are more sensitive than men; moreover, it is a matter

FIG. 371.—SINGLE OLFACTOMETER. (Zwaardemaker.)

of common experience that this sense is easily fatigued, but if fatigued so as to be no longer excited by one kind of odorous substance, it is still in a condition to receive other modalities. Quite similarly, while the persons seated in a poorly ventilated room, are quite unable to perceive the foulness of the air, one who has just entered immediately notices its quality. Furthermore, some persons are absolutely insensitive to certain odors; at least, they fail completely in recognizing their respective qualities.

In this connection, attention should again be called to the fact that the sense of smell is absent in some animals and is very unequally developed in others. For this reason, the osmatic group of animals is commonly divided into a microsmatic and macrosmatic, the latter class including such animals as the dog and rabbit. Clearly, the ability of the dog to follow the trail of his master must depend upon a very acute recognition of individual odors, the stimulating quantity of

¹ Fischer and Penzoldt, Liebig's Annalen, 1887, 131.

which must be infinitely small. In animals of this kind, the sense of smell must, of course, become prepotent in determining their behavior, both volitionally and reflexly.

Qualitative Differences in the Olfactory Sensations.—The modalities of smell are very numerous and their number is increased still further by newly acquired sensations. Thus, a chemist is generally trained to recognize a much larger number of substances than the layman, but even that person whose olfactory impressions have been most minutely associated, is quite unable to classify them in accordance with their qualities. In most cases, one must be content with characterizing them as agreeable or disagreeable. A. von Haller, however, has divided them into *odores suaveolentes*, *odores intermediae* and *odores factores*. In this regard the sense of smell differs very greatly from the others, because it does not permit of at least a general arrangement of these sensations into a fundamental and a complex group. The following classification of Zwaardemaker which is based upon the observations of Linne, tends to overcome this defect in a slight degree by recognizing at least certain vague similarities between them:

1. Ethereal odors, depend upon the presence of such substances as the esters. They are emitted by different fruits.
2. Aromatic odors are given off by such substances as camphor, resinous oils and citron.
3. Fragrant odors, comprise the various odors of flowers and perfumes.
4. Ambrosial odors, are typified by amber and musk.
5. Garlic odors, are emitted by the onion, garlic, sulphur, and the compounds of selenium and tellurium.
6. Burning odors, are given off by benzol, phenol, tobacco smoke and similar substances.
7. Caproic odors, find their origin in the caproic and caprillic acids of sweat, cheese, and the spermatic and vaginal secretions.
8. Repulsive odors, are yielded by many plants, such as *acanthus*.
9. Nauseating or fetid odors, are given off by putrefying substances of animal origin.

A conflict between these sensations arises whenever two odors are permitted to act at the same time. While the result then obtained, is largely dependent upon the odors selected, the strongest most generally predominates in consciousness. At other times, they may alternate with one another without, however, being fused into an intermediate compound sensation. An actual fusion does not result, as a rule, unless they belong to one and the same group of odors. A mixture of two or more odors which presents a modality quite different from those of the fundamental odors, may be effected by such substances as vanillin and bromin, turpentine and xylol, and others.¹ Certain odoriferous substances may also be mixed in certain proportions to annul their individual effects. A neutralization of this kind is obtained by mixing 4 grains of iodoform with 200 grains of balsam Peru.

¹ Nagel, *Zeitschr. für Psych. und Physiol. der Sinnesorgane*, xv.

The Structure of the Taste Buds.—These peculiar bodies are widely distributed through the mucous membrane lining the mouth and pharynx.¹ They are found upon the tip, margins and posterior region of the dorsal aspect of the tongue, but not upon its lower surface. Limited numbers of them may also be detected in the mucosa of the fauces and adjoining regions of the pharynx and epiglottis. In children they are more numerous than in adults, invading even the adjoining regions of the cheeks and posterior fauces. These outlying taste buds atrophy in later years. This retrogression also involves those occupying the median area of the tongue.

The taste buds appear as oval bodies, measuring 80μ in length and 40μ in width. Externally they are enveloped by the cortical reticular cells, while their central portion is occupied by a number of

FIG. 372.

FIG. 372.—DIAGRAMMATIC REPRESENTATION OF CIRCUMVALLATE PAPILLA SHOWING THE POSITION OF THE TASTE-BUDS.

FIG. 373.

FIG. 373.—TRANSVERSE SECTION THROUGH A TASTE-BUD.

A, taste pore; B, spindle-shaped cells of the taste-bud; C, reticular cells; D, nerve fibers terminating among its cells.

closely packed, elongated cells which send their hair-like projections into the depression overlying them. This depression, which is known as the taste-pore, is the seat of the stimulation leading to taste sensations. The nerve fiber enters through the basal pole of the taste-bud and terminates in arborizations among the different gustatory cells. These fibers lose their medullary sheath directly before entering.

It has just been stated that these end-organs communicate with the general cavity of the mouth through the taste-pore. Many of them, however, do not lie directly upon the surface, but occupy a position in the depressions between the different elevations of the mucosa. The tongue, for example, exhibits three types of elevations which, in accordance with their shape, are known as filiform, fungiform and circumvallate papillæ. Those mentioned last are found chiefly upon the posterior aspect of this organ and are beset with an especially large

¹ First described by Loven and Schwalbe in 1867.

number of taste buds. Sometimes as many as one hundred of these may be congregated in the depression encircling a single papilla. It is to be noted especially that they are well protected against the ordinary mechanical stimuli which arise in consequence of the movements of the tongue

The Innervation of the Taste Buds.—In accordance with their wide distribution, it cannot surprise us to find that their innervation can only be accomplished with the help of several nerves. Those directly involved are the lingual nerve, a branch of the inferior maxillary division of the trigeminus, and the glossopharyngeal and vagus nerves. The first innervates the anterior region of the tongue, or about two-thirds of the entire organ; the second the posterior part and root of the tongue as well as the adjoining soft parts, and the third the epi-

FIG. 374.—DIAGRAM SHOWING ORIGIN AND COURSE OF THE NERVE FIBERS OF TASTE.

glottis and mucosa of the larynx proper. It is to be noted, however, that the fibers allotted to the lingual nerve, pursue a double course, *i.e.*, while some of them remain within the system of the trigeminus, others leave it to enter that of the chorda tympani. The latter, in turn, either continue in this system of the seventh cranial nerve (portio intermedia Wrisbergii) or pass over to the glossopharyngeal nerve. It seems certain, however, that the fibers originally allotted to the glossopharyngeus and vagus nerves, pursue a straight course to their respective nuclei in the medulla.

The function of the glossopharyngeus is, of course, quite evident, because cutting this nerve leads to a loss of the sensations of taste in the region innervated by it and eventually to a complete atrophy of the corresponding taste buds. The fact that the chorda tympani takes part in the conduction of taste-impulses, may be evinced at any time by stimulating this nerve as it traverses the tympanic cavity. The usual effect of this procedure is a metallic or sour taste, but some

investigators also claim to have produced sweet and bitter sensations.¹ Much diversity of opinion, however, prevails regarding the central distribution of these fibers. Thus, Krause² states that, the total extirpation of the Gasserian ganglion is followed by a loss of taste in the corresponding anterior region of the tongue. Cushing,³ moreover, has found that this operation never impairs the taste sensations from the posterior part of the tongue. It may be concluded, therefore, that the fibers from this region traverse the petrosal ganglion and enter the sensory nucleus of the glossopharyngeus in the medulla. The fibers from the taste buds of the larynx must necessarily follow the highway of the vagus, while those from the anterior two-thirds of the tongue must for the present be assumed to enter by way of the trigeminus and facial nuclei.

The Activation of the Taste Buds.—When food is taken into the mouth, it is subjected to a mechanical as well as chemical reduction, with the result that it is brought into intimate relation with the largest possible number of taste buds. Substances to be tasted must, of course, be in a fluid state. This end is generally attained with the aid of the saliva which not only acts as a solvent, but also tends to carry the particles into the crevices between the base of the tongue and the fauces, and facilitates their entrance into the furrows around the papillæ in which the taste buds are situated. Clearly, the movements of the tongue are not essential to taste, but materially facilitate the reduction and distribution of the food. It may be concluded, therefore, that the sensation of taste arises in consequence of a reaction between the sapid substance and the protoplasm of the gustatory cells, through the intervention of their hair processes.⁴ It must also be evident that this reaction can only take place if the sapid agent possesses definite chemical properties. It is true, however, that chemically allied bodies need not exhibit identical characteristics in this regard. Thus, sugar, saccharin and lead acetate all give rise to a sweet taste, while the starches do not. In addition, it should also be remembered that sensations of taste may be evoked by substances contained in the blood. Thus, the jaundiced person frequently experiences a bitter taste, while the diabetic perceives sweet. It has also been claimed that sensations of taste may be evoked by electrical means, but not by mechanical or thermal stimuli. Thus, it is usually stated that the anode gives rise to a sour and the cathode to a bitter sensation. This phenomenon has been referred by some experimenters to a direct excitation of the taste buds,⁵ while others contend that it arises only in consequence of electrolytic dissociations at the seat of the electrodes.⁶ At the present time no

¹ Blau, *Berliner klin. Wochenschr.*, xlv, 1879.

² *Münchener med. Wochenschr.*, xlii, 1895.

³ *Bull. of the Johns Hopkins Hospital*, Baltimore, xiv, 1903, 77.

⁴ Zwaardemaker, *Ergebn. der Physiol.*, Wiesbaden, 1903.

⁵ Öhrwall, *Skand. Archiv für Physiol.*, ii, 1891, and Zeynek, *Zentralbl. für Physiol.*, xiii, 1898.

⁶ Hermann, *Grundrisse der Physiol.*, 1872, 337.

facts are at our disposal which could be used to exclude the second view, and hence, we must regard the excitation of the taste buds by inadequate stimuli as not proven,

The Power of Reaction of the Taste Buds. Gustometry.—The acuity of the sense of taste may be tested by bringing solutions of different concentration in relation with different points of the tongue and ascertaining the dilution which barely suffices to incite a sensation. These fluids may be applied either with a camel's hair brush or a dropper, but inasmuch as the tongue is also equipped with tactile, temperature and pain receptors, they must be non-irritating and should be heated to a few degrees below the temperature of the body. Very cold and very warm solutions diminish the sensitiveness of these end-organs. Care must also be taken that the substances selected for these tests, do not activate the olfactory cells, and that they are not spread to other regions of the oral cavity by movements of the tongue.

All sensations of taste are preceded by a definite latent period, which is caused in part by the delayed action of the sense-organs themselves, and in part by the fact that the substances must first be dissolved. Other factors to be controlled are the size of the field stimulated, the length of the period during which the stimulus is allowed to act and the general sensitiveness of the mucous membrane. It is a matter of common experience that the receptive power of the latter is materially altered by habits, such as the use of alcohol and tobacco. The values of the latent period for the tip of the tongue are as follows:¹

Sodium chlorid.....	0.308 sec.
Sugar.....	0.446 sec.
Sulphuric acid.....	0.536 sec.
Quinine.....	1.082 sec.

The Topography of the Sense of Taste.—While the sensations of taste are very numerous, it is possible to arrange them in four fundamental groups, namely, as sweet, bitter, acid and salty. Such modalities as burning, astringent, aromatic and oily are composite in their nature and require the simultaneous activation of the olfactory cells as well as of the sense-organs for touch and temperature. Thus, weak acids give an astringent sensation in addition to a distinct taste of sour, while strong acids amplify the primary impression by a burning sensation. A similar amplification of common sensibility is effected by alum and pepper.

Even the fundamental taste sensations may be combined to give a fused or compound effect. Thus, weak solutions of sweet and salty substances may yield a sensation of flatness or alkalinity, and a weak sensation of sweet may be completely neutralized by the addition of a few grains of sodium chlorid. Quite similarly, the addition of sugar to lemon juice diminishes the acidity of the latter and gives rise to a mixed sensation in which the components may be clearly recognized.

¹ Kiesow, Wundt's philos. Studien, ix, x and xii, 1894-96; also Zeitschr. für Psych. and Physiol. der Sinnesorgane, xxvii, 1901.

It is also to be noted that the tongue is not equally sensitive to all four primary tastes. By far the greatest acuity for sweet prevails upon the tip of tongue, while bitter is most clearly perceived upon its posterior aspect in the vicinity of the circumvallate papillæ. The acuity for sweet decreases gradually from before backward and that for bitter in the opposite direction. The sour taste is most highly developed in the central fields of the marginal regions of the tongue, and the salty taste in its antero-lateral regions. Peculiarly enough, these different sensibilities may be varied by means of certain drugs. Thus, we find that the application of a solution of cocain to the surface of the tongue first of all diminishes our acuity for the compound impressions, so that acids produce merely a sour taste without any astringent or burning admixture.¹ Next in order follow the fundamental sensations, namely, bitter, sweet, sour and salty. A very similar effect may be produced by chewing the leaves of *gymnemna sylvestre*. In this case, the sensations of sweet and bitter are destroyed, while the acid and salty tastes, as well as the general sensibility, are not impaired.²

These facts recall to our minds the interesting question regarding the specificity of the taste buds, it being entirely probable that the four fundamental qualities of taste are mediated by four different types of end-organs. Thus, Öhrwall has shown that certain papillæ react only to particular kinds of sapid substances. Of the total number of 125 examined, 98 could be activated by different substances. Of this number, 60 yielded three modalities of taste sensations, while 12 gave sweet and acid, 12 only acid, 7 bitter and acid, 4 sweet and bitter, and 3 only sweet. In addition, it has been pointed out that parabrombenzoic sulphinid gives rise to a sensation of sweet when placed upon the tip of the tongue, and to a sensation of bitter when applied to its posterior surface. Quite similarly, sodium sulphate tastes salty upon the tip of the tongue and bitter upon its posterior region.

B. GENERAL INTEROCEPTORS, APPETITE, HUNGER AND THIRST

Appetite.—It has been mentioned above that in the lower forms the sensations of smell and taste occupy the position of exteroceptors, while in the higher animals, they assume more especially the function of interoceptors. In addition, the latter group also embraces a large number of peculiar internal sensations, chief among which are the sensations of appetite, hunger and thirst. Regarding the first, it has commonly been held that it is merely a mild form of hunger and is not mediated by separate receptors. Cannon and Washburn,³ on the other hand, seem to differentiate sharply between these sensa-

¹ v. Amrep, Pflüger's Archiv, xxi, 1880, and Knapp, Archiv für Augenheilk., 1885.

² Edgeworth and Hooper, Nature, xxxv, 1887, 565.

³ Amer. Jour. of Physiol., xxix, 1912, 441.

tions and characterize appetite as a pleasurable mental state, which has its origin in an excitation of the mechanisms for taste and smell, while hunger constitutes a more disagreeable and stronger sensation which arises in certain receptors in the walls of the stomach. Carlson¹ who has studied this subject more recently, adheres to this classification.

These general contentions, however, do not aid us very materially in establishing a physiological basis for these sensations; in fact, it must be admitted that we know practically nothing regarding them. Besides the sensory element imparted to them by the senses of smell and taste, they also possess a gastric component introduced by the simultaneous excitation of some sensory unit of the gastric mucosa. Thus, it is a matter of common experience that the ingestion of food blunts the appetite as well as the hunger, while both are evoked by total abstinence. Still, certain conditions may be introduced which lead to a dissociation of these sensations. For example, while a prolonged fast very frequently diminishes and destroys all the pleasurable sensations connected with the thought of food, the sensation of hunger may persist for some time thereafter. Again, the mere passage of the food through the esophagus may satisfy the appetite, in spite of the fact that the hunger contractions of the stomach continue. Quite similarly, the gradual emptying of the stomach after a meal usually restores the appetite at a time when actual hunger is not experienced as yet.

The contrary sensation of appetite is an aversion to food, which arises whenever the gastric reservoir is well filled or when the body as a whole is unable to assimilate a particular kind of food. Thus, it frequently happens that we acquire an aversion to fat or gelatin in spite of the fact that these substances possess a distinct nutritive value. As in the case of appetite, this sensation arises in special interoceptors; but also embraces a gastric element.

Hunger.—The sensation of hunger is primarily projected to the region of the stomach, but may also make itself felt by the more general sensations of mental and bodily fatigue and functional depression. To begin with, there is a local feeling of emptiness in the stomach which is intensified in the course of time into a painful sensation. Furthermore, this sensation shows a definite intermittency and may be temporarily abolished by the ingestion of even indigestible material. These three facts seem sufficient to disprove one of the hypothesis which holds that hunger is a general sensation and is caused by certain changes in the metabolism of the tissues, particularly in that of the nervous tissues.² Another view is that hunger is caused by the stimulation of certain afferent nerves in the gastric mucosa in consequence of the distention of the glands by accumulated secretion (Beaumont). No facts can be mentioned in support of this hypothesis other than that sensations of hunger are generally followed by a sudden out-

¹ Carlson and Braafladt, *Am. Jour. of Physiol.*, xxxvi, 1914, 153.

² Turro, *Zeitschr. für. Psych. und Physiol. der Sinnesorgane*, xlv, 1911.

pouring of gastric juice. A third hypothesis is that hunger is due to the stimulation of certain afferent nerves in the stomach by the contraction of its musculature. In support of this view might be mentioned the contracted state of the empty stomach, the periodic peristaltic waves passing over it, the abolition of this sensation after the introduction of indigestible substances, and the rumbling gastric noise produced when this sensation is experienced. Cannon and Washburn have proved that the sensation of hunger occurs simultaneously with increases in intragastric pressure. In nervous persons, however, and especially in women, loud rumbling noises are frequently heard without being associated with this sensation.

Carlson¹ has repeated these observations upon a man with a gastric fistula established after the occlusion of the esophagus by a cicatrix. It is stated that there is a fairly close correspondence between the duration of the contractions and the duration of the subjective sensation of hunger. A similar relationship was noted between the intensity of this sensation and the strength and rapidity of development of the contractions. Moreover, while a distinct sensation of hunger could be produced by suddenly inflating a balloon placed in the stomach, it could not be evoked by tactile stimulation of the gastric mucosa. The peripheral genesis of this sensation, therefore, seems established, although no definite data have been obtained regarding the nervous mechanism involved in it.

Attention should also be called at this time to the continued sensation of hunger experienced by the diabetic patient which prompts him to eat superfluous amounts of food. A similar condition frequently results in persons whose lower intestine has been made to open through the abdominal wall in order to relieve an obstruction in the rectum or neighboring parts (Carcinoma). Under this condition the pangs of hunger are experienced even when the stomach is comfortably filled with food. In view of these facts, it might be well to recognize two types of hunger, namely, *gastric hunger* which is present normally, and general or *somatic hunger* which is brought into play under unusual conditions.

Thirst.—The sensation of thirst is specifically referred to the pharynx, unless there is a general scarcity of water, in which case this local sensation is augmented by fatigue, anguish, pain and suffering. In the first instance, the sensation is evoked in a circumscribed region of the pharynx situated directly in the path of the currents of air ebbing back and forth between the outside and the lungs. It is conceivable that the terminals of the glossopharyngeus nerve are specifically adapted to perceive variations in the water content of the cells lining this area, because thirst is experienced as soon as the latter becomes dry and even at a time when the body as a whole is abundantly supplied with water. A local moistening then suffices to give relief without that water is actually taken into the stomach. But, these lining cells may

¹ Am. Jour. of Physiol., xxxi, 1912, 175.

also become dry when the general water content of the body is depreciated, because water is constantly transferred by them to the respiratory air. While a local moistening also gives relief in this case, it is not lasting and can only be made so by taking water into the stomach. When water is long withheld, all the tissues become water-starved so that the simple sensation of *pharyngeal thirst* becomes augmented by more distressing symptoms, such as pain and a bodily and mental anguish and discomfort. It is conceivable that these sensations arise in the receptors allotted to the different tissues. If this assumption is correct, a second variety of thirst must be recognized which may be designated as *general or tissue thirst*. The testimony of those persons, however, who have been without food and water for long periods of time, tends to show that these symptoms of extreme discomfort and pain disappear in the course of time, so that death by starvation need not necessarily be accompanied by extreme suffering.¹

¹ Hertz, *The Sensibility of the Alimentary Canal*, London, 1911; Sven Hedin, in his travels through Thibet, alludes to many cases of self-imposed abstinence by the Holy Men of Brahma.

SECTION XXI

THE SENSE OF HEARING

CHAPTER LXII

THE CAUSE AND CHARACTER OF THE SOUND WAVES

The Cause of Sound Waves.—Sound waves arise in consequence of the vibration of elastic bodies. If a metal plate is suspended in space and its central area is struck with the end of a rod, it suffers a displacement of its constituents which permit it to deviate in the direction of the stroke. Having attained its extreme position in this direction, it immediately swings back toward the opposite side, and so on until it has again attained its equilibrium. These deviations of the plate in turn give rise to a vibration of the air surrounding it, because those molecules which lie directly in its path will be alternately condensed and rarefied. In this way, the vibrations of the sonorous body are transferred into undulations of an elastic medium, formed by the air. The first are stationary and the second progressive in their nature.

Vibrations of a sonorous body may be either transverse, as in a string, or longitudinal, as in a rod. The undulations in a medium, however, must of necessity be longitudinal, because only forward impulses or pushes can be communicated from one molecule to another. Thus, sound is conveyed onward by an undulatory or wave-like motion in air, similar to that exhibited by particles of water during the translation of a wave. In water, however, the different particles move in a circle, while in air they move in a straight line, backward and forward, in the direction in which the sound is projected.

The initial energy of the undulations in air is gradually reduced as they pass away from the sonorous body, so that the sound diminishes constantly until it becomes completely neutralized. This reduction, however, takes place at a more rapid rate than is theoretically suggested by the law of inverse squares. The reason for this discrepancy is that vibration leads to friction and friction to heat, generated, of course, at the expense of the initial energy.

Sound waves may also be propagated by media other than air, in fact, in many instances with much better results. Thus, they pass along rods of wood with the greatest ease, and also along cords and wires. Practical use has been made of this fact in the construction

of the earlier forms of stethoscopes (Laennec) which usually consisted of a wooden cylinder perforated through its axis and enlarged at its ends. Furthermore, their initial energy may be protected against loss by sending them through narrow tubes, because they are then no longer propagated as concentric spheres, but are reflected from the walls of the tube. We shall see later on that this is true of the sound waves traversing the external auditory meatus.

Any sound produced near at hand, seems to reach our ears instantaneously. In reality, however, there is a distinct interval between the moment of its production and the moment when it produces its stimulation in the internal ear. This latency is caused in part by a certain sluggishness of the receptor, and in part by the fact that sound waves require time for their propagation through the medium. A distant locomotive or steam boat is seen to discharge a certain volume of steam through its vibrator long before the sound produced thereby actually reaches our ears, and the flash of lightning is seen long before

FIG. 375.—LAENNEC STETHOSCOPE.

the thunder is heard. While altitude, temperature and the general character of the medium have much to do with the propagation of the vibrations from molecule to molecule, it may be said that the velocity of sound is 340 m. in a second. Its speed, however, is proportional to its intensity, *i.e.*, loud sounds travel more rapidly than those possessing a low quality. Through water sound is propagated at the rate of about 1450 m. in a second, and through wood at the rate of about 13,000 m. in a second.

• Sound waves may be reflected and refracted. In the ear we deal chiefly with reflections from curved surfaces in which the reflection takes place on the opposite side of the perpendicular, drawn to the point of impact of the incident wave. The angle of reflection invariably equals the angle of incidence, and both occupy the same plane. In the ear we have curved surfaces which are constructed in such a way that the inclinations of the planes of which any curved surface is composed, gives rise to a convergence of the sound waves. Thus, the external ear of man possesses a curvature arranged to reflect these undulations into the auditory meatus. The same is true of the ear trumpet and of the flexible stethoscope. Both appliances collect the sound waves by means of their cup-shaped free ends and reflect them into the meatus.

Noises and Sounds.—It is not always easy to distinguish between a noise and a sound. In general, however, it may be said that the former consists either of a brief vibration, as may be produced by the discharge of a cannon, or of a mixture of vibrations as may be caused by the wheels of a carriage. It lacks, therefore, a definite wave length and

regularity. A true or musical sound arises in consequence of a sustained vibration, and possesses an euphonious character by reason of its relatively fixed and uniform rate. The difference between noises and true sounds may be well illustrated by means of sirenes placed upon a rotating disc. If the openings through which the air is blown, are placed at regular distances from one another, the result is a sound of definite pitch, quality and loudness, while if they are arranged in an irregular manner, the result is a noise.

FIG. 376.—FORM OF WAVE MADE BY TUNING FORK.

Musical sounds result in consequence of the vibration of such bodies as strings, rods, plates, bells, membranes and reeds. The waves produced by them, however, do not affect our organ of hearing in a like manner, because they differ from one another in their pitch, intensity or loudness, and quality or timbre.

(a) The pitch or tone of a sound is determined by the rapidity of vibration of the sonorous body and the number of undulations produced by it. The greater their number, the shorter must be their wave length and hence, the higher the pitch of the sound. Thus, if these oscillations recur at the rate of 500 in a second, their time of vibration is $\frac{1}{500}$ of a second.

FIG. 377.—TO ILLUSTRATE THE CONCEPTION OF DIFFERENCES IN PITCH AND IN AMPLITUDE OR INTENSITY.

In A, three pendular or sinus curves of the same period or pitch, but with different amplitudes. In B, three pendular or sinus curves of the same amplitude, but with different periods. (After Auerbach.)

(b) The intensity or loudness of a sound is referable first of all to the amplitude of the vibrations of the sonorous body. Thus, if the bass string of a piano is struck with slight force, it will be seen to execute a series of vibrations of small amplitude, which give rise to a sound of low audibility. If this same string is then struck more vigorously, the amplitude of the vibrations will be much greater and the sound much louder. These changes in the intensity of a sound may also be noted as the vibrating body gradually returns into its position of absolute rest. In the second place, the loudness of a sound is determined by the striking force of the waves, because the latter is inversely proportional to the square of the distance

of the vibrator from the ear and to the density or elastic quality of the medium. Thus, the voice becomes remarkably feeble on top of a mountain and is much stronger in a calm atmosphere.

(c) The quality, timbre, stamp or color of a sound is the product of a variety of factors; primarily, however, of the form of the movement of the sonorous body and of the form of the waves produced by it. Thus, a sound of a certain pitch and intensity emitted by a piano, is quite different from that of a violin or of the phonating organs of man. If these sound waves are examined more closely, it will be found that they appear in two distinct forms, namely, as a simple or pendular and as a compound or non-pendular type. If we permit the pointed end of a simple reed vibrator to record its excursions upon the smoked paper of a kymograph, the record so obtained will show perfectly symmetrical deviations from the line of rest, because the pointer has swung back and forth across the midline in a uniform manner. A compound wave, on the other hand, presents asymmetrical deviations, which, however, may be perfectly periodic.

FIG. 378.—SCHEMA BY HELMHOLTZ TO ILLUSTRATE THE FORMATION OF A COMPOUND WAVE FROM TWO PENDULAR WAVES.

A and B, pendular vibrations, B being the octave of A. If superposed so that e coincides with d^0 and the ordinates are added algebraically, the non-pendular curve C is produced. If superposed so that e coincides with d' the non-pendular curve D is produced. (Howell.)

Fundamental Tones and Overtones.—If the string of a musical instrument is set into transverse vibration by plucking it, a certain sound will be emitted, the pitch, quality and loudness of which will depend not only upon the length and the thickness of this vibrator, but also upon the force with which it is displaced. If the string is now firmly held midpoint between its two ends, the vibrations of each half per unit of time will be doubled. Furthermore, if the string is divided in this way into three segments, each division will vibrate with a frequency three times greater than that of the entire

string. Fourier has proved that every sonorous body, when made to vibrate as a whole, also exhibits vibrations of its different segments. For this reason, every compound wave should really be considered as the product of the fusion of a number of simple waves, *i.e.*, if a sonorous body yields, say, 100 vibrations in a second, it also gives off a series of notes in the ratio of 1, 2, 3, 4, etc. The former give rise to the so-called fundamental tone and the latter to the partial tones, overtones or harmonies.

Inasmuch as all musical instruments, inclusive of the mechanism set aside for the production of the human voice, send forth fundamental tones as well as overtones, the sounds emitted by them,

FIG. 379.—TO ILLUSTRATE THE MECHANISM OF THE FORMATION OF OVERTONES.
(Helmholtz.)

In *a* the string vibrates as a whole, giving its fundamental tone; in *b*, *c*, and *d*, its halves, thirds and fourths are vibrating independently. When a string is struck, plucked, or bowed these movements may happen simultaneously and the fundamental note due to the vibration of the whole string is combined with the notes due to the vibrations of aliquot parts, the overtones. The combination gives a compound wave whose form and musical quality vary with the number and relative strength of the overtones.

are really compound in their nature and not simple. The trained ear is capable of analyzing these sounds, but naturally, they arrive at the tympanic membrane as compound waves and are not separated into their component wavelets. In other words, the tympanic membrane is not activated by individual series of molecules of air vibrating with different frequencies, but by whole waves, the form of which varies in accordance with their component wavelets.

Reinforcement and Interference of Sound Undulations.—If two stones are thrown into the water at some distance from one another, the two systems of wavelets produced around their points of contact, fre-

quently interfere with one another so as to give rise either to a reinforcement or a neutralization of the individual undulations. In quite the same manner the simultaneous transfer of two sounds through the same medium may give rise to waves which may be either the sum total or the difference of the two systems of undulations. The complete neutralization of the two sets necessitates, of course, the coming together of the condensed molecules of one system with the rarefied molecules of the other system.

If two tuning forks, the vibrations of which differ slightly per unit of time, are being sounded simultaneously, the two systems of undulations must interfere with one another. Consequently, the sound emitted by them must vary from moment to moment, becoming louder when they reinforce and softer when they neutralize one another. This constitutes the phenomenon of "beats." If the difference in the number of vibrations per unit of time is increased, the effect produced on the ear becomes increasingly disagreeable. The sound then assumes a harsh grating character and is said to be discordant or dissonant. Helmholtz states that the dissonance assumes an intolerable character, when the "beats," or the difference in the vibration frequency of two sounds, reaches 33 to the second.

In the absence of "beats" the general sound becomes consonant or harmonic. This implies that the two sets of undulations correspond in rhythm and amplitude, enabling them to be combined into an evenly balanced compound wave. It must be evident, therefore, that a perfect consonance can only be gotten if the two sets of waves are identical in character. An almost complete consonance is also obtained if a sound is elicited in conjunction with its octave. It is a well-known fact that two sounds possessing a numerical relationship of 2:1, 4:1, etc., must be closely allied. Thus, if the first is designated as *C*, the second is called *CI*, and the interval between them an octave. If we now strike the octave note of the second and then the octave of this one, it will be found that their entire series of octaves or eighth notes become fused into a sound which gives an agreeable sensation. Other intervals giving consonance are the following:

- 1:2 octave
- 2:3 fifth
- 3:4 fourth
- 4:5 major
- 5:6 minor third
- 5:8 minor sixth
- 3:5 major sixth

Sympathetic Vibration or Resonance.—If the end of the handle of a vibrating tuning fork is placed upon a table or other elastic body, its vibrations are immediately communicated to a large area of this vibrator. Moreover, since the latter generally vibrates synchronously with the tuning fork, its sound will be intensified. In a similar way, it is possible to produce vibrations in a certain string of a piano

by simply striking a note of the same character upon some other instrument. The piano answers back with a note very similar to that received by it from the distance. Also, if a certain note is struck in the vicinity of a series of tuning forks, only that tuning fork will answer which possesses the same periodicity of vibration as the primary sound. These phenomena are made possible by the property of sympathetic vibration or vibration of influence. As has been pointed out, the transmission of the sonorous undulations may be effected in two ways, namely, by direct contact, and by the transfer of the waves through air without actual contact. It is to be noted, however, that while elastic bodies may be set into vibration by neighboring bodies and media, they cannot be activated unless their own periodicity corresponds precisely to that of the activator. Thus, a string possessing a vibratory quality of 125 in a second, will not be affected by vibrations in air of 100 to the second.

FIG. 380.—
KÖNIG'S RE-
SONATOR.

Helmholtz has devised an apparatus, called the resonator, by means of which it is possible to analyze sounds in accordance with their properties of sympathetic vibration. It consists of a spherical capsule made of copper or brass. Its two opposite sides are perforated. Through one of these the sound is conducted into the interior of the resonator and from here through the opposite opening into the external auditory meatus. König has introduced an important modification of this appliance by constructing it of two hollow cylinders. By sliding these telescopically into one another, the size of this capsule may be either increased or decreased. If the rubber tube attached to its outlet is now introduced into the auditory meatus of one ear while the other ear is closed, the sounds entering through the opposite orifice, will appear stifled with the exception of the one corresponding to this resonator. This particular one sounds out clearly from among the confused monotone of the others.

If resonators of varying size are employed, it is possible in this way to determine the presence or absence of the different tones or overtones represented by them. Any given sound may thus be separated into its components. This power of analysis is also possessed by the auditory apparatus, or rather, by the constituents of the organ of Corti of the internal ear. As Ohm has stated: every motion of the air which corresponds to a composite mass of musical tones, may be reduced into their simple pendular vibrations, and each single vibration corresponds to a simple tone, sensible to the ear and having a pitch determined by the periodic time of the corresponding motion of the air. These facts suggest that the organ of Corti acts in the manner of a resonator, its different cellular elements being adjusted to conform to these simple vibrations. The manner in which this activation is brought about will be discussed in a succeeding chapter.

CHAPTER LXIII

THE EXTERNAL AND MIDDLE PORTIONS OF THE EAR

The Pinna and Auditory Meatus.—The organ of hearing may be divided into three parts, namely, into the *external ear*, including the pinna or auricle and auditory meatus, the *middle ear*, or tympanum, and the *internal ear*, or labyrinth. The first two are accessory structures and merely serve to direct the undulations in air to the receptor, formed by the organ of Corti of the cochlea. The pinna or auricle is the funnel-shaped expanse of the auditory meatus, consisting essentially of yellow elastic tissue covered with skin. The cap-shaped depression in its center is known as the concha.

The external ear is especially adapted to collect the sound waves and to reflect them through the auditory meatus upon the tympanic membrane. It may be taken for granted, however, that it is not a particularly important part, because many animals lack the pinna entirely without any apparent impairment in the acuity of their hearing, and a person whose pinna has been cut off, can hear almost as well as previously. In many animals, the pinna is beset with muscles which are under the control of the will and are employed to change its shape and position and to turn it in the direction of the sound waves. In many instances, the ears are moved in divergent directions which must naturally give a different reflection on the two sides

and hence, also impart a different quality to the sound as heard by the two ears. This faculty is especially developed in horses and rodents. Aquatic animals are in possession of a valve-like mechanism for closing the auditory meatus and many terrestrial animals are capable of enlarging the concha. In man these muscles are evidently of very little importance, because they are retrogressive and cannot, therefore, play a significant part in ascertaining the direction from which the sound is received. The latter faculty seems to originate in the conjugate deviation of the eyes toward the side from which the sound waves have been projected.

FIG. 381.—DIAGRAMMATIC REPRESENTATION OF THE DIFFERENT PARTS OF THE EAR.

1, Pinna; 2, external auditory meatus; 3, ear drum; 4, middle ear containing the ossicles; 5, Eustachian tube; 6, vestibule of the internal ear; 7, auditory nerve; dividing into two branches, one of which innervates the cochlea and the other, the semi-circular canals; 8, parotid gland.

The external auditory meatus of man is a tubular passage 21–26 mm. in length, 8–9 mm. in height, and 6–8 mm. in width. It pursues a slight spiral course forward, inward and upward, but may be straightened very easily by pulling the pinna upward and backward. This is made possible by the fact that the wall of this canal is cartilaginous and movable for a distance of about one-half inch, while internally to this point it becomes osseous. The delicate skin lining this canal contains numerous sebaceous and ceruminous glands which furnish the cerumen, a yellowish wax-like secretion, possessing a bitter taste and peculiar odor. This secretion is lubricating and protective in its function, because it prevents, in conjunction with the hairs, the

entrance of dust and larger foreign particles. Its excessive formation and subsequent drying frequently lead to the formation of chips and plugs which greatly impair the passage of the sound waves, thereby diminishing the acuity of hearing.

The Middle Ear or Tympanum.

—The middle ear consists of an irregular cavity hollowed out of the petrous portion of the temporal bone. It is broader above and behind than below and in front, and is shut off from the external auditory meatus by the eardrum or tympanic membrane. Anteriorly, it communicates with the pharynx by means of a long and narrow tube which is known as the Eustachian tube, while posteriorly, it is connected with the complex system of small cavities in the mastoid bone, known as the mastoid antrum and mastoid cells.

Its inner wall, which is formed by the bony septum of the internal ear, is perforated in two places. Inasmuch as one of these openings is oval in shape and the other round, they are designated as the fenestra ovalis and fenestra rotunda. Both are closed by a membrane, the outer surface of which lies in contact with the air of the tympanum, while their inner surface borders upon the lymphatic fluid filling the labyrinthine spaces. The tympanic cavity is occupied by three small bones known as the ossicles, which are arranged in series between the inner surface of the eardrum and the outer surface of the membrane closing the fenestra ovalis. These ossicles are freely suspended in this space and are held in position by ligamentous bands attached to different points of the wall, as well as

FIG. 382.—DIAGRAMMATIC REPRESENTATION OF THE MIDDLE EAR OR TYMPANIC CAVITY.

1, External auditory meatus; 2, the ear drum or tympanic membrane; 3, malleus, with its manubrium resting against the internal surface of the ear drum; 4, incus; 5, stapes resting against the membrane of the fenestra ovalis; 6, vestibule of the internal ear; 7, fenestra rotunda; 8, Eustachian tube; 9, saccule; 10, central canal of the cochlea; 11, utricle; 12, musc. tensor tympani.

by two muscles, known as the *musculus tensor tympani* and the *musculus stapedius*.

The Tympanic Membrane or Eardrum.—The tympanic membrane is stretched across a cartilaginous ring which is placed obliquely in the inner end of the auditory canal. It possesses a somewhat oval shape and is tilted at an angle of 40° in a direction from above and without to a point within and below, this peculiarity in its position enabling it to present a much larger surface to the sound waves. The membrane itself is 9.5–10 mm. in length and 8 mm. in breadth. Its thickness measures 0.1 mm. and its area 50 mm. It consists of three layers, its middle coat being formed of fibrous tissue which is enveloped externally by a delicate layer of skin, and internally by the mucous membrane, lining the general cavity of the tympanum. The fibers of the median coat are chiefly arranged in a radial direction,

FIG. 383.—MEMBRANA TYMPANI, AS SEEN WITH THE OTOSCOPE. (Heusman.)

but some of them are also adjusted circularly around its center. The latter are especially numerous in the region where this membrane is joined to the ring of cartilage.

The inner surface of the eardrum lies in contact with the handle, or manubrium, of the first ossicle, commonly known as the hammer-bone or malleus. This process is securely fastened to its median layer, the *membrana propria*, by an overlapping of its circular fibers. When observed through the external meatus, the line of contact between the malleus and the eardrum is sharply outlined by an opaque ridge which commences near its upper anterior margin and extends downward and backward to a point slightly below its center. The surface of the eardrum is not flat, but convex toward the outside. Its apex points inward, this central depression, or umbo, being caused by the inward traction of the tip of the manubrium. It will be seen, therefore, that the different radial fibers uniting this process with the membrane, are arranged as arches around a common center.

It need scarcely be emphasized that the external auditory meatus plays the part of a tube tending to conserve the character of the sound waves. They are deflected from its walls into the pit of the funnel-shaped tympanic membrane, but since the sides of the latter are convex, their amplitude must be diminished, while their striking force is increased. In this way, this membrane is set into vibration in complete harmony with the undulations in the air. Moreover, since it is small in size, it is able to move as one whole and with a definite periodicity. The latter peculiarity is of particular value, because it prevents the magnification of certain overtones to the exclusion of others. In addition, its structure and position are such that it is able to offer a certain resistance to the oscillations of this system which causes the latter to cease almost as soon as the sound has been completed. The dampening effect is of great functional importance, because it keeps these parts in a state of readiness to receive new vibrations.

FIG. 384.—VIEW OF THE MEMBRANA TYMPANI AND AUDITORY OSSICLES FROM THE INNER SIDE. (Schäfer.)

m, Malleus; *i*, incus; *st*, stapes; *py*, pyramid, from which the tendon of the stapedius muscle is seen emerging; *ts*, tendon of the tensor tympani cut short near its insertion; *la*, anterior ligament of the malleus; the anterior process (processus gracilis) is concealed by the lower fibers of this ligament; *ls*, superior ligament of the malleus; *li*, ligament of the incus; *ch*, chorda tympani nerve passing across the outer wall of the tympanum.

The Ear Bones or Ossicles.—The connection between the eardrum and the membrane of the fenestra ovalis is formed by three bones which are known as the malleus, incus, and stapes.

The *malleus* or hammer bone, is 8–9 mm. in length and possesses an average weight of 23 mgrs. It consists of a rounded head, grooved on one side for its articulation with the incus, a short massive neck and a long handle, or manubrium. The latter is securely fastened in the tissue of the eardrum and presents two processes, one of which is known as the *processus brevis* and the other as the *processus gracilis*. The former presses against the eardrum above the umbo, while the latter extends into the Gasserian fissure in the wall of the tympanum. The malleus is held in place by three ligaments, a superior, anterior and posterior. The first of these holds the head of this bone against the roof of the tympanic cavity, while the second and third secure its neck in a position near the anterior wall of this space. Besides serving as supports, these ligaments also force this bone to rotate around a perfectly definite axis. This is true especially of the anterior and posterior ligaments which tend to fix its neck portion as if it were placed in a sling. Consequently, the inward movement of the eardrum and manubrium must cause the head of this bone to move outward, while their outward movement must force the latter inward.

The *incus* or anvil bone, weighs about 25 mgrs. and possesses a shape somewhat similar to that of a bicuspid tooth, its heavier upper portion being hollowed out for

the reception of the head of the malleus. This articulation is effected in a plane situated somewhat above the brim of the eardrum. This ossicle presents two processes, the largest of which measures 4.5 mm. and the other 3.0 mm. in length. To begin with the former extends downward, parallel to the manubrium of the malleus, but suddenly turns inward to enter into articulation with the stapes. The short process is fastened to the posterior wall of the tympanum by a thick ligament which, however, gives rise to only a partial fixation of this bone.

The *stapes* or stirrup bone, is only 2.5 mm. in length and weighs about 3 mgrs. Its base is oval in shape and is fastened to the membrane of the fenestra ovalis by means of a number of radial fibers of connective tissue. This foramen measures 3 mm. in length and 1.5 mm. in width.

The Movements of the Ossicles.—It need scarcely be emphasized that the function of the ear bones is to convert the vibrations of the eardrum into vibrations of the membrane closing the fenestra ovalis. This implies that the undulations in air are converted into oscillations of the lymphatic fluid filling the spaces of the internal ear.¹ The latter then activates the constituents of the organ of Corti. In endeavoring to analyze the action of the ossicles it must be remembered that the manubrium of the malleus is firmly anchored to the eardrum and must, therefore, move in harmony with the latter. This fact may be demonstrated in a very convincing manner by placing the umbo under the ocular of a microscope,² inserted through a perforation in the upper wall of the tympanum. When measured with the help of a micrometer, these movements are seen to attain a maximal amplitude of about 0.2 to 0.7 mm.

Inasmuch as the neck of the malleus is fixed by the anterior and posterior ligaments, the inward movement of its manubrium must give rise to an outward deviation of its caput. This simple pendular motion, however, cannot become excessive, because the malleus executes at the same time a rotatory movement around its long axis. The outward inclination of the caput of the malleus in turn enforces a movement of the head of the incus in the same direction. At this very moment the latter is turned as a whole around the axis formed by its short process, while its long process is raised and is forced inward against the stapes, pushing the latter more deeply into the foramen ovale. The outward movement of the eardrum produces a movement of these ossicles in the opposite direction. Helmholtz has compared the malleus-incus articulation to the joints of a Breguet watch-key, possessing a row of interlocking teeth which force the stem of the watch in one direction, but prevent its revolution in the opposite direction.

It will be seen, therefore, that this series of bones acts in the manner of a bent lever, the fulcrum of which is placed at the tip of the short process of the incus, while the power arm extends from here through the tip of the manubrium, and the load arm, from here through the tip of the long process of the incus. This arrangement is repre-

¹ Helmholtz, Pflüger's Archiv, i, 1869, 34.

² Golitzer, Archiv für Ohrenheilkunde, i, 1864, 59, also see: Mach and Kessel, Ber., Akad. der Wissensch., Wien, lxi, 1874, 221.

sented in the adjoining diagram (Fig. 385). When combined into one single mass, these bones act upon the axis *a-b*, the manubrium *c* and stapes *d* then pursuing precisely the same course, inward as well as outward (Fig. 386). This system is rendered especially sensitive by the fact that a large part of the total mass of the malleus and incus comes to lie above their axis of rotation *a-b*, so that their upper portions are made to act as a counterpoise for the parts situated below this axis. The latter constitute the real lever, sensitized, as has just been stated, by this counterpoising weight. It should be noted, however, that the oscillations of the stapes possess a smaller amplitude than those of the eardrum, the relationship between them being as

FIG. 385.

FIG. 385.—TO ILLUSTRATE THE LEVER ACTION OF THE EAR BONES.

M, the malleus; *e*, the incus; *a-b*, the axis of rotation; *a*, short process of incus abutting against the tympanic wall; *a-p*, the power arm; *a-r*, the load arm of the lever. (McKendrick.)

FIG. 386.

FIG. 386.—SCHEMA TO ILLUSTRATE THE WAY IN WHICH THE EAR OSSICLES ACT TOGETHER AS A BENT LEVER IN TRANSMITTING THE MOVEMENTS OF THE TYMPANIC MEMBRANE TO THE MEMBRANE OF THE FENESTRA OVALIS.

1, The handle of the malleus; 2, the long process of the incus; 3, the stapes; *a-b*, the axis of rotation. The arrows indicate a movement inward of the tympanic membrane. (Howell.)

0.04 mm. to 0.4 mm. The force, however, with which they strike against the fenestra ovalis, is increased in the proportion of 2 to 3, because the length of the arms of the lever formed, on the one hand, by the manubrium, and, on the other, by the long process of the incus, is as 3 to 2. Furthermore, since the area of the eardrum is about twenty times as large as that of the membrane closing the foramen ovale, the initial energy is concentrated in this way upon an area twenty times smaller than that exposed to the sound waves. Consequently, the force of these waves is augmented $\frac{3}{2} \times 20 = 30$ times, when projected against the fenestra ovalis.

It is also of importance to remember that this system is not given to after-vibration, because it is made to act under a considerable

resistance which finds its origin in several conditions. Among these we have cited the peculiarities in the structure and position of the eardrum and also the unusual characteristics of the lever formed by the ossicles. In addition, Helmholtz has called attention to the fact that the articulation between the malleus and incus may be broken at any time by unusually strong inward movements of the eardrum.¹ The head of the malleus is then forced outward so far that the incus cannot follow it. Doubtlessly, this dislocation serves to protect the internal ear against sounds of extraordinary striking force. As we shall see later, an additional factor of safety has been provided in the shape of the stapedius muscle, the contraction of which pulls the head of the stapes over so that this bone presses more firmly upon the membrane closing the fenestra ovalis, thereby diminishing its vibratory qualities.

The Eustachian Tube.—A membrane, such as the eardrum, is capable of developing the most perfect vibrations only when the pressure upon its two surfaces is equal. If the tympanic cavity were absolutely closed, the air contained therein would be absorbed in the course of time, establishing a rarefaction which in turn would give rise to an inward bulging of the eardrum, and a diminution in its oscillatory power. Under ordinary conditions, however, a result of this kind is obviated by the fact that the tympanum is connected with the pharyngeal cavity by means of a membranous communication, known as the Eustachian tube. While the pharyngeal end of this channel is kept closed under ordinary conditions, it may be opened at any time by the act of swallowing which involves a contraction of the *musculus tensor veli palatini*. This permits of an interchange of air in both directions. The closure of this orifice results immediately upon the cessation of this muscular effort on account of the elastic recoil of its valve-like lips, situated inside the ostium.

If we enter a tunnel in which the pressure is above that of the atmospheric air, the tympanic membrane is forced inward. This gives rise to a peculiar local sensation of pressure as well as to a diminution in the acuity of hearing. The tube is then opened by the act of swallowing which allows the required amount of air to rush into the tympanum. In a similar way, a diminution in the atmospheric pressure gives rise to an outward displacement of the eardrum which is remedied immediately by permitting air to escape from the tympanum. A condition of the first kind may be set up very easily by swallowing during the act of inspiration while the lips and nostrils are held shut. The opposite condition may be produced by swallowing during expiration while the lips and nostrils are kept closed.

Although this tube serves chiefly as a means for the ventilation of the tympanum, it also forms a natural outlet for excess secretions. Both functions are greatly impaired during catarrhal affections of the

¹ This hypothesis has been criticized by von Frey (*Pflüger's Archiv*, cxxxix, 1911, 548) upon the ground that the malleus and incus are not united by a true joint, but are more or less ankylosed.

pharynx involving this tube, as may be gathered from the diminution in the acuity of hearing then commonly experienced. In many instances, these simple catarrhal affections pave the way for suppurative processes which spread from the lining of the tympanum to the ossicles, destroying them in part or causing them to become ankylosed. The exudations formed in the course of this process most commonly burrow their way through the eardrum, but without permanently destroying the oscillatory qualities of this membrane. The greatest danger of an infection of this kind lies in the fact that it may spread to the adjoining mastoid cells and, unless the latter are freely drained, give rise to a septic infection of the neighboring meninges.

The Inherent Muscles of the Ear.—Besides the different muscles attached to the pinna, the ear also contains two muscles which are intimately concerned with the transmission of the sound waves through the tympanum. These muscles are the tensor tympani and the stapedius. The former is placed in a long furrow above the Eustachian

tube and is inserted by means of a long tendon into the neck of the malleus directly below the axis of rotation of this bone. It is innervated by fibers derived from the trigeminus and relegated to the otic ganglion. When this muscle contracts, it pulls the eardrum inward, thereby placing it under a greater tension. This fulfills two purposes, namely to accommodate the drum to sounds of higher pitch, and to lessen its vibratory power whenever sounds of great intensity are received. It need scarcely be mentioned that a sound of high pitch can only be transferred in its true form if the tension of the drum is increased sufficiently to correspond to its wave-length. In the second place, it must be evident that a tense membrane is more resistant than a flaccid one and cannot, therefore,

be made to vibrate so easily. For this reason, the tensor tympani muscle may also be regarded as a protective means against the activation of the organ of Corti by sounds of unusual intensity. Consequently, its function is very similar to that of the iris which, by the contraction of its radial fibers, lessens the size of the pupil, thereby preventing the entrance of a bundle of light of injurious intensity to the retina.

The stapedius muscle arises from the inner wall of the tympanum near the fenestra ovalis. Its tendon passes forward and is inserted upon the posterior aspect of the neck of the stapes. On contraction it pulls this bone over in a lateral direction so that the hinder part of its base is pressed more firmly into the membrane closing this foramen. In accordance with the degree of its deviation, it increases the tenseness of this membrane until its vibration is finally prevented

FIG. 387.—DIAGRAM ILLUSTRATING THE ACTION OF THE STAPEDIUS MUSCLE.

A, state of relaxation; B, state of contraction; s, stapes; m-s, musc. stapedius.

altogether. The stapedius muscle, therefore, serves the same purposes as the tensor tympani, *i.e.*, it accommodates the membrane of the fenestra ovalis to high sounds, and prevents those of unusual intensity from reaching the internal ear. The motor fibers of this muscle are derived from the facial nerve.

Both muscles react in consequence of reflex stimuli which appear to be derived from the auditory nerve,¹ whence they are transferred in the medulla to the aforesaid motor paths. These stimuli arise at the very beginning of the different sounds and subject these membranes to constant changes. Some persons are capable of contracting the tensor tympani voluntarily.²

CHAPTER LXIV

THE INTERNAL EAR OR LABYRINTH

General Structure.—The general cavity of the internal ear, or *osseous labyrinth* is hollowed out of the petrous portion of the temporal bone. It consists of three parts, namely, the vestibule, the semicircular canals and the cochlea. It is lined throughout with thin periosteum. This entire space is filled with a lymphatic fluid, called the *perilymph*. Suspended in this fluid is a membranous reproduction of the osseous labyrinth, which in turn is filled with a lymphatic fluid, called the *endolymph*. The outer surface of the latter keeps at varying distances from the wall of the bony cavity. The space between them is occupied by perilymph and is transected by ligamentous bands and fibers which hold the membranous labyrinth in place. In the vestibular part of the osseous labyrinth, this membranous tube shows two enlargements which are known respectively as the *utricle* and *sacculæ*. The former is directly continuous with the membranous tubes of the semicircular canals and the latter, with the membranous canal of the cochlea.

It will be brought out later on that the semicircular canals are concerned solely with the sense of equilibrium, while the cochlea mediates the sense of hearing. For the present, therefore, we must confine ourselves to a study of the latter structure. The cavity of the internal ear is separated from that of the tympanum by a bony wall, which is perforated in two places to form the fenestra ovalis and the fenestra rotunda. Both openings are closed by membranes, the outer surfaces of which lie in contact with air, while their inner surfaces border upon the perilymph of the labyrinth. It has also been pointed out that the vibrations in air are eventually converted into vibrations of lymph at

¹ Henson, Pfüger's Archiv, lxxxvii, 1901, 355.

² Mangold, Pfüger's Archiv, cxlix, 1913, 539.

the fenestra ovalis. From here these oscillations spread throughout the perilymph of the vestibule and pass toward the semicircular canals as well as toward the cochlea. In most cases, however, they fail absolutely in activating the sense-organs of equilibrium in the utricle and ampullæ of these canals, because the latter do not lie in the direct course of these waves, and are not specifically adapted to them. The cochlea, on the other hand, turns its funnel-shaped basal portion directly toward the vestibule and into the path of these oscillations.

Besides, this structure gives lodgment to the sense-organ which is specifically set aside for their reception.

The Osseous Canal of the Cochlea.—The central chamber of the labyrinth, or vestibule, measures 5 mm. in diameter and communicates anteriorly with the cochlea. The latter is a cone-shaped structure, measuring 9 mm. across at its base, and 5 mm. from its base to its apex. The tip or cupola of the latter is directed outward and slightly forward and downward. It contains a canal which is twisted upon itself two and one-half times in the manner of the shell of a snail. This canal measures about 33 mm. in length. It is largest at its base, where it measures about 2 mm. in diameter. The central core around which it is wound, is known as the modiolus. The latter consists of a central spongy portion which is pierced by a tube with its various collaterals for the reception of blood-vessels and the

FIG. 388.—DIAGRAMMATIC VIEW OF THE INTERNAL EAR.

1, Tympanic cavity; 2, Eustachian tube; 3, incus; 4, stapes; 5, vestibule of the internal ear (perilymph); 6, utricle; 7, central canal of the cochlea; 8, scala vestibuli; 9, saccule; 10, endolymphatic duct between saccule and utricle; 11, ampulla of semicircular canal; 12, canalis reuniens; 13, scala tympani; 14, helicotrema; 15, fenestra ovalis.

fibers of the cochlear branch of the auditory nerve. A bony plate, the lamina spiralis, projects from this central mass of bone almost horizontally into the lumen of the cochlear canal, winding round into its tip in the manner of a circular staircase. It partially divides the lumen of this canal into two compartments or scalæ; this division being made complete by a membranous septum which stretches straight across from the end of the bony lamina to the opposite wall of the canal. This is the so-called basilar membrane. Below the latter, we have the scala tympani and above it, the scala vestibuli. The cochlear canal as a whole is placed in such a way that its vestibular scala faces the foramen ovale, while its tympanic scala is directed toward the foramen rotundum. These tubes communicate with one another

through a small orifice in the tip of the cochlea, which is known as the helicotrema.

FIG. 389.—MEMBRANOUS LABYRINTH OF THE RIGHT SIDE, SEEN FROM THE EXTERNAL SURFACE.

1, Utricle; 2, superior semicircular canal; 3, posterior semicircular canal; 4, external semicircular canal; 5, saccule; 6, endolymphatic canal, with 7 and 7', its two branches, and 8, its vestibular cul-de-sac; 9, cochlear canal, with 9', its vestibular and 9'', its terminal cul-de-sac; 10, canalis reuniens of Hensen. (*American Text-book of Physiology.*)

These two scalæ, therefore, are separate tubes. The scala vestibuli ascends from the vestibule into the tip of the cochlea, while the scala

FIG. 390.

FIG. 390.—CROSS-SECTION THROUGH THE COCHLEA, SHOWING THE DIFFERENT WINDINGS OF THE CANALS.

M, modiolus, with the branches of the cochlear division of the auditory nerve; S, spiral ganglion; b, basilar membrane with the organ of Corti; s-t, scala tympani; c, central canal.

FIG. 391.

FIG. 391.—DIAGRAM ILLUSTRATING THE VIBRATION IN OPPOSITE DIRECTIONS OF THE MEMBRANES CLOSING THE FENESTRA OVALIS AND ROTUNDA.

S, stapes; o, fenestra ovalis; r, fenestra rotunda.

tympani descends from here to the fenestra rotunda. Both are filled with perilymph, and the vibrations set up by the oscillations

of the stapes are propagated through them in the direction from the vestibule to the fenestra rotunda. This is of importance, because it enables the membranes closing the aforesaid foramina, to vibrate in unison. In other words, an inward movement of the membrane of

FIG. 392.—DIAGRAM OF A TRANSVERSE SECTION OF THE COCHLEA.

Sc.V, scala vestibuli; Sc.T, scala tympani; C.Chl, canalis cochlearis; Lam.sp, lamina spiralis; Gg.sp, ganglion spirale; n.aud., auditory nerve; m.R, membrane of Reissner; Str.v, stria vascularis; Lg.sp, ligamentum spirale; t.t, lymphatic epithelioid lining of basilar membrane on the tympanic side; m.b, basilar membrane; Org. C, organ of Corti; L.t, labium tympanicum; lb, limbus; L.v, labium vestibulare; m.t, tectorial membrane. (After Foster.)

the fenestra ovalis gives rise to an outward movement of the membrane of the fenestra rotunda. If no provision had been made for this interchange of pressure within the internal ear, the membrane of the

fenestra ovalis could not vibrate properly, because it could not overcome the high resistance resident in this chamber.

The Membranous Canal of the Cochlea.—It has just been shown that the osseous canal of the cochlea is bisected by the spiral lamina and the basilar membrane attached thereto. Directly above the membranous part of this partition, a second membrane stretches obliquely across the lumen of the vestibular scala which thus cuts off an angular space, known as the central canal of the cochlea or scala media. The lower boundary of the latter is formed by the basilar membrane (*lamina basilaris*), its outer boundary by the bony wall of the cochlea, and its upper by the aforesaid *membrana vestibularis* or membrane of Reissner. This space is filled with endolymph and forms, therefore, the cochlear continuation of the membranous labyrinth. Special

FIG. 393.—THE ORGAN OF CORTI IN THE GUINEA PIG. (Nakamura.)

attention, however, should be directed to the colony of modified cells situated upon the basilar membrane, the free surfaces of which border upon the endolymph of this tubule. These cells form the organ of Corti which is most directly concerned with the reception of the sound waves in the form of vibrations of the lymph filling these scalæ. The manner in which this transfer is effected will be more fully discussed later on.

The Structure of the Organ of Corti.—The basilar membrane forming the floor of the central canal of the cochlea, gradually increases in width from the base to the apex of the cochlea. The width of the osseous lamina, on the other hand, decreases in a corresponding measure. Thus, Henson¹ states that its breadth amounts to only about 0.041 mm. below, but to 0.495 mm. above. Its total length measures 33.5 mm. Its substance is formed by a homogeneous ground-substance containing numerous straight fibers which are suspended in a radial manner between the tip of the bony lamina and the liga-

¹ Archiv für Ohrenheilkunde, vi, 1873.

mentous tissue upon the external wall of the cochlear canal. Retzius¹ has estimated the number of these fibers at 24,000.

The entire cochlear canal is lined by a single layer of cuboidal cells which also extend across the under surface of the membrane of Reissner. The body of the latter consists of an extremely thin layer of connective tissue derived from the periosteal lining of the scala vestibuli.² It is to be noted especially that the cells situated upon the basilar membrane, possess a most peculiar appearance. A single cross-section of this particular area presents two rod-shaped cells

FIG. 394.—DIAGRAMMATIC VIEW OF THE ORGAN OF CORTI, THE SENSE CELLS, AND THE ACCESSORY STRUCTURES OF THE MEMBRANOUS COCHLEA.

A, inner rods of Corti; B, outer rods of Corti; C, tunnel of Corti; D, basilar membrane; E, single row of inner hair (sense) cells; 6, 6', 6'', rows of outer hair (sense) cells; 7, 7', supporting cells of Deiters. The ends of the inner hair cells are seen projecting through the openings of the reticulate membrane. The terminal arborizations of the cochlea nerve fibers end around the inner and outer hair cells. (*Testut.*)

which are separated at their bases, but come together above in the manner of the sides of a roof. These cells are usually referred to as the inner and outer rods of Corti. The triangular space situated in between this double row of inclined cells, is known as the tunnel of Corti. Internal to the inner rod of Corti is a single epithelial cell which sends a brush of short and stiff projections into the endolymph. On the outer side of the outer rod of Corti are three or four cells which are slender in shape and also carry hair-like processes.³ They are supported by the so-called cells of Deiters. External to these hair

¹ Das Gehörorgan der Wirbeltiere, ii, 1884.

² Stöhr, Anat. Anzeiger, 1907, und Kolmer, Archiv für mikr. Anatomie, lxx, 1907.

³ Scott, Jour. of Anat. und Physiol., 1909, also see: Nakamura, Über die Myelinoid-Substanz in den Haarzellen des Cortischen Organes, Berlin, 1914.

cells are several tall columnar cells which rapidly decrease in height until they have attained the simple character of the general lining of this tubule. Practically the entire surface of the organ of Corti is covered by a thick fibrillated membrane, the tectorial membrane, which takes its origin upon the upper surface of the limbus and sweeps almost transversely through the lumen of this canal.

The Function of the Organ of Corti.—These different rows of cells are continued spirally into the tip of the scala media. It has been estimated that there are more than 2500 inner and 13,000 outer hair cells. Their total number is generally given as at least 16,000. We have every reason to believe that these hair cells are the elements which receive the sound waves, this assumption being based principally upon their general appearance and position. In the second place, it is noted that the cochlear branch of the auditory nerve ascends through the modiolus and directs its fibers radially through the spiral lamina into the organ of Corti. Near the base of the lamina these fibers traverse a ganglion, known as the ganglion spirale. The cells of this structure are bipolar, their peripheral branches being continued onward into the basilar membrane where they lose their medullary sheath and enter the epithelium in the region of the inner hair cells. Some of these fibers terminate here, while others continue onward and cross the tunnel of Corti to enter the region of the outer hair cells. In this region they terminate as fine filaments which invest the lower poles of the corresponding cells of Deiters.

The fact that the rods of Corti are not present in birds, which doubtlessly possess a very keen sense of hearing, shows that these elements are not essential to hearing. The same conclusion may be drawn from the fact that their number is altogether too small to be able to receive the large number of sound waves to which we may be subjected. Retzius, for example, estimates their total number at less than 10,000, of which 5600 are inner rod cells. This exclusion of the rods as direct factors in the reception of the sound waves, leaves us free to localize this function in the hair cells. In accordance with Helmholtz, it may then be held that the latter play the part of sympathetic resonators which are capable of reducing musical sounds into their components.

The Activation of the Organ of Corti.—In accordance with a suggestion of Hensen, it has been advocated by Helmholtz that the constituents of the organ of Corti are activated from below by the sympathetic vibrations of the radial fibers imbedded in the basilar membrane. It is believed in this case that the vibrations of the perilymph in the scala tympani are transmitted to these fibers and that the latter in turn stimulate the hair cells above them. This contention harmonizes with the fact that the basilar membrane contains about 24,000 of these fibers, and that their length gradually increases from the base to the tip of the cochlea (135μ to 234μ). Thus, the fibers in the base of the cochlea would be adapted to high notes, and those near the heli-

cotrema to deep notes. In accordance with this view, it must be assumed that each fiber has its own periodicity of vibration and is capable of analyzing the simple waves of a particular compound wave. The simultaneous vibration of a number of these fibers would of course give rise to several sensations which are then fused in consciousness. No definite statements can be made at the present time regarding the manner in which the vibrations of these fibers are transferred to the hair cells and endings of the auditory nerve.¹

Those physiologists who claim that these fibers are not sufficiently long to serve as efficient resonators, hold with Max Meyer² that (a) the analyzer is the basilar membrane itself, or (b) the vibrations in perilymph are directly transferred to the hair cells through the intervention of the endolymph of the central scala. The first view meets with the same objections as the resonance theory of Helmholtz. The second, on the other hand, has several points in its favor, because it ascribes a perfectly definite function to the peculiar hair-like prolongations of these cells. It is conceived that these processes float free in the endolymph of the central canal and are, therefore, in the best possible position to receive the vibrations set up in this fluid in consequence of the transferred oscillations of the lymph in the adjoining scala vestibuli. These hairs, therefore, serve the purpose of a battery of resonators, capable of resolving the compound vibrations into their simple constituents. In this case, the tectorial membrane is assumed to play merely the part of a dampener similar to the felt pad upon the strings of a piano.

In support of the second view Ayers³ asserts that the membrana tectoria, as seen in ordinary preparations, is an artefact and is nothing more than a matted mass of hairs which in reality form a waving plume extending from the surfaces of the hair cells through the endolymph to be inserted upon the crest of the ridge immediately beside the internal border of the organ of Corti. These long extended processes are activated by the vibrations in endolymph and transfer their impulses directly to the cells and adjoining nerve endings.

To make this list complete, it might be mentioned that some physiologists believe that the resonating organ is the tectorial membrane itself which, however, vibrates only in segments and solely along its thin margin.⁴ Its vibrations are communicated to the hair cells, the processes of which are in this case regarded as short stubby bristles.

Whichever theory we may feel inclined to accept, it must be evident that the final analysis of the sound waves is accomplished in the auditory realm of the cerebral cortex. Subsequent to their association they are projected to the place in the medium from which they appear

¹ Baginsky, *Virchow's Archiv*, xciv, 1883, 65.

² *Zeitschr. für Pyc. und Physiol. der Sinnesorgane*, xvi, 1898; also see: Ewald, *Pflüger's Archiv*, lxxvi, 1899, 147, Yoshii, *ibid.*, 1909.

³ *Journal of Morphology*, 1892.

⁴ Ebner, in *Köllicker's Handb. der Gewebelehre*, iii, 1902, 958.

to have been derived. This localization, however, involves not only a judgment regarding the intensity of the sounds as individually perceived by the two ears, but also an analysis of the position of the head and of the conjugate deviation of the eyes. Naturally, a median localization of the sound necessitates an equally intense activation of the two receptors and a lateral localization, an unequal activation. In the latter case, our judgments as to right and left, are surprisingly accurate, although we are frequently in error as to whether the sound has arisen in front or behind us, above or below us. Consequently, our ears act in the manner of the two eyes during binocular vision, our judgments regarding the special relationship of objects being derived from the two visual fields. It seems doubtful, however, that our judgments regarding the direction and distance of sounds are much less exact than those pertaining to our visual impressions. Thus, a ventriloquist plays upon the judgment of other persons by altering the quality of his vocal sounds in such a way that they imitate the peculiarities of those sounds which he desires to impart to his hearers. He thus makes use of perfectly normal mental concepts of sounds to produce an erroneous impression.

Conduction of Sound Waves by the Cranial Bones.—It has been pointed out that the organ of Corti is activated by the vibrations in the neighboring endolymph and perilymph, and that the latter are ordinarily the result of the oscillation of the ossicles in consequence of sound waves. But, conditions may also arise in space which allow of a direct transfer of these waves to the bones of the cranium and in turn evoke a vibration of the lymph in the internal ear. Thirdly, it is possible to produce these vibrations by bringing a resonant body, such as a tuning fork, in direct contact with one of the cranial bones. If placed upon the region of the interparietal suture, the localization will be median in character, for the reason that both ears are now affected in an equal measure. If one of the ears is then protected by placing the tip of a finger into the auditory meatus, the sound is immediately diverted into this ear, and, if both ears are shielded in this way, again into the midline of the cranium.¹ In explaining this phenomenon, it must be remembered that the oscillations of the lymph resulting in consequence of this direct transmission of the sound waves, are also transferred to the ossicles and to the eardrum. If the ear is now held shut, the initial energy of the vibration in lymph is prevented from being spent in this way, and hence, must be able to act with greater intensity upon this particular receptor. In all these cases, however, the projection is intracranial, as against the extracranial localization noted whenever the sound waves are permitted to enter in the normal way through the auditory meatus.

Subjective sensations of sounds, such as ringing in the ears, most commonly arise in consequence of a local or general hypersensitiveness of the nervous system. This condition leads to spastic contractions

¹ Weber, *Archiv für Ohrenheilkunde*, xviii, 1882, 130.

of the tensor tympani. Humming or rushing noises most generally have their origin in circulatory disturbances (hemic murmurs). A common entotic phenomenon is the audibility of the heart beat when the left side of the head is placed upon a pillow. This position increases the resonance of the left internal ear in a greater degree than that of the right.

The Limits of Hearing. Auditory Fatigue.—While inheritance and training play an important part in determining our range of the appreciation of sounds, it is usually stated that the human ear cannot be activated by musical tones possessing a lesser vibratory rate than 24 to 30 in a second. Some persons, however, are capable of perceiving sounds of only 16 vibrations to the second. Below this limit mere sensations of pressure are produced, although some of these low sounds may give rise to high overtones which are clearly recognizable. The upper limit of audibility of musical sounds is generally placed at 40,000 double vibrations in a second. Beyond this point, the notes give rise to unpleasant sensations rather than to true sounds and cannot be used in music. At about 60,000 they become inaudible. A convenient way in which the range of hearing may be tested is to strike steel rods of varying vibrating frequency (König).

It is commonly accepted that rhythmically repeated or long continued sounds eventually give rise to a condition of auditory fatigue. In many cases, however, this fatigue is only apparent and is due rather to inattention. Thus, the ticking of a watch may become inaudible to us, because other matters temporarily occupy our attention. Intense sounds produce a peculiar deafening effect, rather than a true fatigue.

The Perception of Noises.—Noises form a physical as well as a physiological entity, because they lack the rhythmic and harmonic character of musical sounds. In spite of this fact, however, they possess a definite pitch, quality and intensity. Helmholtz has advocated the view that they are mediated by a special receptor formed by the sensory epithelium of the utricle and saccule. Exner,¹ on the other hand, states that they are also received by the organ of Corti, and that they activate a large number of resonators, in contradistinction to the musical sounds which affect only particular ones. Being a believer in the Helmholtz resonance theory, Exner holds that they stimulate the radial fibers of the basilar membrane.

¹ Pfüger's Archiv, xiii, 1876, 228.

SECTION XXII

THE SENSE OF EQUILIBRIUM

CHAPTER LXV

THE SENSE OF POSITION. STATIC SENSE

The Otolithic Cavity.—This organ is usually represented by a membranous saccule which is placed in the integument in free communication with the outside. Its epithelial lining is beset with long hair-like processes, the tips of which are weighted with small concretions of calcium carbonate, known as otoliths. Many of these granules rest free among the hairs. The general structure of these otocysts has led physiologists to believe that they are quite unable to oscillate in unison with the vibrations in the surrounding medium and cannot, therefore, play a part in the reception of sounds. For this reason, it is now commonly held that they are concerned with equilibration and more particularly with the perception of position than with that of motion; *i.e.*, with the “static” rather than with the “dynamic” sense.

This conclusion has a definite experimental basis, because if the otolithic material is removed, the animal shows disturbances in its position and movements. Thus, the destruction of the otocyst in crustaceans gives rise to a tilting of the head toward the side on which this injury has been effected. Quite similarly, if made to move, this animal invariably moves about in a circle, returning finally to the place from which it started. The same result may be obtained by cutting the nerves innervating these organs. It seems, therefore, that the otocyst and otolith should really be named statocyst and statolith respectively.¹ This nomenclature seems to be indicated the more, because Kreidl,² has succeeded in varying the equilibration of the crustacean palemon by changing the contents of its statocyst. At the time of molting this animal fills its statocystic cavities with granules of sand to tide it over this particular period. If

FIG. 395.—THE OTOLITHIC CAVITY SHOWING THE LINING CELLS WITH THEIR HAIR-LIKE PROLONGATIONS AND THE OTOLITHS.

¹ Von Buddenbrock, Sitzungsber., Akad., Heidelberg, 1911.

² Sitzungsab., Akad. zu Wien, cii, 1893, 149.

it was placed at this time in the vicinity of finely pulverized iron, it used this material instead of the sand, with equally beneficial results. Inasmuch as its otostatic cavities are situated at the base of the antennæ in free communication with the outside, the gravity of the iron could be varied by means of magnets. Whenever this was done, the animal immediately displayed pronounced disturbances in its movements, leading to a loss of its proper position in space. Very similar disorders have been observed by Prentiss¹ in the larvæ of lobsters which had been prevented from obtaining a temporary substitute for their statolithic material by placing them in filtered sea water. Streeter,² moreover, has shown that tadpoles do not acquire the power of equilibration until the sixth day after fertilization, *i.e.*, not until the auditory vesicles have made their appearance. The destruction of one of these organs gives rise to disturbances in its equilibrium which may be rendered even more pronounced by the removal of both.

The Utricle and Sacculæ.—While we have seen that the otolithic cavity of the invertebrates is not an organ of hearing, it cannot be denied that it serves as the precursor of the organ of hearing of the higher vertebrates. The auditory sac, arising as a depression in the epiblast near the hindbrain, becomes separated from the main tube, but does not enter into direct communication with the outside. It gradually develops into the variegated membranous labyrinth, consisting eventually of the central canal of the cochlea, the sacculæ, utricle, and the semicircular canals. In the lower vertebrates the cochlea is absent, the first indication of it being presented by the cysticula of the bony fish. Kreidl,³ however, believes that this organ is still too rudimentary to react to sounds; instead, he supposes the latter to be received by the cutaneous sense-organs in consequence of vibrations set up in the surrounding water. It should be noted, however, that the fish are in possession of a statolithic sac to which one or more semicircular canals are attached. The development of the latter immediately suggests that these animals are also equipped with a dynamic sense of equilibrium.

Beginning with the terrestrial animals, the cochlea develops more rapidly, it being present in an elementary form in the amphibia and reptilia and in its more complete spiral form in birds. In the latter, the central canal of the cochlea is united with the sacculæ as well as with the other endolymphatic spaces. The labyrinth attains a structure comparable to that of man, only in the higher mammals. Situated directly within the osseous vestibule, we have two vesicular enlargements, namely, the sacculæ and utricle. The former attains a length of about 3 mm. and a width of 2 mm. It is placed very close to the orifice of the scala vestibuli of the cochlea. In the direction of the

¹ Bull. Mus. of Comp. Zoology, Harvard Univ., xxxvi, 1901.

² Jour. of Exp. Zoology, iii, 1906, 543.

³ Pflüger's Archiv, lxiil, 1896, 581. The contrary view is held by Zenneck, Pflüger's Archiv, xcv, 1903, 346.

latter it tapers into a narrow duct, measuring 1 mm. in length and 0.5 mm. in height. It finally connects with the central canal of the cochlea a short distance above its expanded lower extremity. The other pole of the saccule communicates with the utricle by means of the ductus endolymphaticus. The utricle is irregular in shape and measures 6-7 mm. in length and 5 mm. in breadth. It gives origin to the semicircular canals. Of particular importance to us at this time is the so-called recessus utriculi, a blind forward projection from the main cavity which contains the macula acustica. This area is formed by auditory epithelium which is beset with hair-like processes carrying otolithic crystals, and is innervated by fibers from the auditory nerve. A similar patch of sensory epithelium is contained in the saccule.

Three views have been held regarding the function of the macula utriculi and macula sacculi, namely (a) that they are the recipients of the sound waves, (b) that they mediate irregular vibrations or noises, and (c) that they serve the purpose of statolithic organs. The first contention may be discarded, because it has now been thoroughly established that the cochlea is fully capable of taking care of this function. The second view is based merely upon assumptions and need not be discussed further. By exclusion, therefore, this discussion may be restricted to the view of Brener,¹ which holds that these structures inform us regarding the position of the head when at rest or when the entire body is engaged in making progressive movements in one direction or another. It is conceived that the otolithic, or rather, statolithic crystals evoke stimulations by means of their weight resting upon the neighboring hair-like processes. This weight, of course, is not objective, but is lessened somewhat by the fact that it is exerted in a medium of endolymph. At any time when the head is tilted, their lines of gravity

FIG. 396.—NERVE-ENDINGS UPON THE INTRAFUSAL MUSCLE-FIBERS OF A MUSCLE-SPINDLE OF THE RABBIT. MODERATELY MAGNIFIED. METHYLENE-BLUE PREPARATION. (*Dogiel.*)

a, Large medullated fiber coming off from 'spindle' nerve and passing to end in an annulo-spiral termination on and between the intrafusal fibers; b, fine medullated fiber coming off from the same stem and dividing. Its branches, c, pass towards the ends of the muscle-fibers and terminate in a number of small localized arborizations, like end-plates.

¹ Pflüger's Archiv, lxxviii, 1897, 596.

are shifted, so that the different hairs are mechanically acted upon with varying force. Furthermore, it should be noted that the maculæ acusticæ occupy different planes in space so that they are affected differently by one and the same position, or progressive movement.

These statolithic receptors supplement the function of the receptors in the ampullæ of the semicircular canals which, as will be shown later, mediate the sensations of rotatory motion and are, therefore, primarily concerned with the production of the dynamic sense. In both cases, these sensations give rise to reflexes which are essential for the maintenance of the equilibrium. Obviously, these reflexes initiate first of all certain muscular movements, which are executed in compensation for these static and dynamic sensations. In last analysis, however, the static and dynamic senses are compound in their nature, because they depend not only upon the sensations derived from the corresponding sensory structures of the labyrinth, but also upon those

FIG. 397.—ORGAN OF GOLGI FROM HUMAN TENDO ACHILLIS. CHLORID OF GOLD PREPARATION. (*Ciaccio.*)

m, Muscular fibres; *t*, tendon-bundles; *g*, Golgi's organ; *n*, two nerve-fibres passing to it.

obtained from the retinæ, from the cutaneous receptors, and, as will be shown later on, from the deep receptors situated in the muscles, joints and tendons.

It is also to be noted that these organs of equilibrium are thoroughly protected against all direct influences from without, *i.e.*, their activation can only be effected by changes arising within the animal itself. For this reason, the static and dynamic sense-organs are commonly regarded as belonging to the proprioceptive system of receptors. Furthermore, since the static and dynamic senses are really compound senses, because amplified and perfected by sensations received from other sense-organs, such as the retinæ and the cutaneous corpuscles, their development actually necessitates a harmonious interaction between different exteroceptors and proprioceptors.

The Muscle Spindles.—It is a well-known fact that the muscles and tendons as well as the lining of the joints and the deep skin are

supplied with a type of sense-organ, the exclusive function of which appears to be to give information regarding the position of our limbs and body as a whole. The one contained in muscle-tissue, is formed by one or more muscle fibers which are permeated by lymph-spaces and are enveloped in a sheath which is made up of several layers of fibrous tissue. The nerve fiber entering this structure, winds spirally around these fibers and eventually terminates in small platelets upon their surfaces. In tendinous tissue this sense-organ appears as an arborization of delicate nerve-filaments upon the surfaces of the individual strands of tissue. This arrangement enables the fibers of the muscle to exert a certain pressure upon these nerve-endings, and to produce impulses which experience has taught us to interpret in terms of a definite degree of contraction of the muscle or of the position of the part moved by it. This central association which, as we have seen, is effected by the cerebellum, constitutes the muscle-sense. These sensations, however, do not amplify merely the sense of position, but also that of motion, because the muscles undergo constant changes.

CHAPTER LXVI

THE SENSE OF MOVEMENT—DYNAMIC SENSE

The Semicircular Canals.—The membranous semicircular canal occupies from one-third to one-fifth of the entire lumen of the osseous canal. The space intervening between its outer wall and the inner surface of the bony canal, is filled with perilymph and the suspensory bands which hold the membranous tube in place (Fig. 388). In cross-section the latter presents an oval or elliptical outline, and is expanded into a cavernous space very shortly after it leaves the utricle. At this particular point it possesses a diameter about twice as long as that of its remaining portion. This enlargement which is known as the ampulla, occupies very nearly the entire lumen of the osseous canal and lies in close contact with the wall of the latter at the convexity of the semicircle. It gives lodgment to the sensory epithelium mediating dynamic sensations. The latter are conveyed from here to the center by the vestibular branch of the auditory nerve.¹

In cross-section each ampulla presents a transverse prominence which is known as the crista acustica. This ridge projects far into the lumen of this passage and is beset with the sensory epithelium. The latter differs from the flat lining of the remaining portion of the semicircular canal in that it consists of elongated columnar cells which are

¹ Ewald, *Physiol. Untersuchungen über das Endorgan des Nerv. Octavus*, Wiesbaden, 1892.

surmounted by long tapering processes. These hair-like extensions measure about 0.03 mm. in length and project straight into the endolymph. Somewhat above the basement membrane these cells terminate in a rounded extremity which lies in relation with the finely

FIG. 398.—DIAGRAMMATIC REPRESENTATION OF THE STRUCTURE OF THE AMPULLA OF A FISH.

The columnar cells of the crista acustica (c) are beset with hair-like prolongations which float free in the endolymph. N, nerve fibers leading away from ampulla.

subdivided axis cylinders of the vestibular nerve fibers. The space between the lower poles of these hair-cells and the basement membrane is taken up by the fiber cells of Retzius¹ which present themselves as long filaments showing at one point a nuclear enlargement.

FIG. 399.—FIGURE SHOWING THE POSITION OF THE THREE SEMICIRCULAR CANALS IN THE SKULL OF THE PIGEON. (Ewald.)

The Relative Position of the Semicircular Canals.²—The three osseous semicircular canals take their origin from the vestibular enlargement of the labyrinth, while the three membranous canals arise from the utricle. Since two of these tubes, namely, the two vertical ones, become confluent before they again return to this space, they possess only five orifices in all. The three canals of each side are arranged in such a way that they cover three distinct planes which lie approximately at right angles to one another. The *external or horizontal canal* measures 15 mm. in length and traverses a plane at right angles to the mesial plane of the body (Fig. 399E). It occupies, therefore, a horizontal position when the head is held erect. Its ampulla is located anteriorly.

The *anterior or superior canal* is placed nearly vertical at an angle of 45° to the mesial plane of the body (A).

¹ Biolog. Untersuchungen, vi; also: Brener, Sitzungsber., Akad. zu Wien, cxii, 1903.

² First called attention to by Cyon (1873), Brown (1874), and Mach (1875).

It is 19 mm. in length and rises to a higher level than any other part of the labyrinth, its location being indicated upon the upper surface of the petrous portion of the temporal bone by an arched prominence. Its ampulla is situated in front. The *posterior or inferior canal (P)* is also placed nearly vertical at an angle of 45° to the mesial plane of the body but in such a way that it inclines toward the superior canal at a right angle. It measures 22 mm. in length and its ampulla lies at the back part of the vestibule.

A comparison of the planes of these canals with those of the canals on the opposite side shows immediately that the left anterior covers the same plane as the right posterior, and the right anterior that of the left posterior. It is evident, therefore, that they supplement one another. In this connection, attention should also be called to the fact that the vestibular division of the auditory nerve divides into two branches, namely, into the ramus utriculo-ampullaris and the ramus sacculo-ampullaris. The former innervates the utricle and ampullæ of the superior and horizontal canals, and the latter, the saccule and ampulla of the posterior canal.

FIG. 400.—DIAGRAM TO SHOW THE POSITION OF THE SEMICIRCULAR CANALS TOWARD ONE ANOTHER.

The Effects of Lesions of the Semicircular Canals.—The first accurate investigations pertaining to the function of the semicircular canals, have been made by Flourens¹ upon pigeons, these animals having been selected for this purpose because their labyrinth is more accessible to operative procedures than that of the mammals. It was found first of all that the destruction of the vestibule and adjoining semicircular canals does not impair the sense of hearing, but merely evokes disorders of equilibration, which, in accordance with Goltz,² are the result of an abolition of function and not of a loss of stimulation. Thus, it could easily be shown that the unilateral destruction of the canals renders the animal unable to maintain its position. If it is made to move, it sways and repeatedly tumbles toward the side of the injury. The head remains tilted toward the operated side and is even held in an inverted position. These symptoms disappear in the course of three or four weeks so that the animal

FIG. 401.—ABNORMAL POSTURE OF PIGEON, IN WHICH THE LABYRINTH HAD BEEN EXTIRPATED ON ONE SIDE FIVE DAYS PREVIOUSLY. (Ewald.)

¹ Compt. rend., lii, 1828; also: Vulpian, Leçons, sur la physiol. du syst. nerveux, Paris, 1866.

² Pflüger's Archiv, iii, 1870, 172.

is again able to fly and to walk, although it continues to suffer from a certain loss of tonus of its muscles, principally of those of the head and trunk on the side opposite to the injury.

The destruction of the canals on the two sides gives rise at first to a complete loss of equilibrium, so that the animal can neither walk nor fly unless supported. It tends to assume a quiet attitude, but when made to move, executes violent forced and incoherent movements which may even cause its destruction. Its muscles are abnormally flaccid and the joints unusually limber. So small a weight as 20 grams attached to its bill or neck, suffices to keep the head permanently in the most abnormal position, and to make it sway in the direction of the weight. These disorders gradually disappear in the course of a few weeks. The animal learns to walk again by making use of the sensations of sight and touch. The muscular weakness, however, persists and losses of equilibrium may be brought about at any time later on by bandaging the eyes.

These defects may be localized and restricted to single planes of the body by destroying only one of these canals. Thus, the loss of, say the horizontal canal, invariably causes the pigeon to make forced movements of the head in the horizontal direction, but any unusual excitation immediately leads to more general rotary movements of the entire body. The length of time during which these symptoms remain in evidence, depends upon the location and extent of the lesion; at all events, it does not suffice to destroy solely the bony canal or to let the perilymph escape through a fistulous opening. These defects are quickly compensated for, provided the membranous canal is left intact. Decided symptoms can only be produced by opening the latter widely and as close to the ampulla as possible.

The destruction of the labyrinth in amphibia is followed by symptoms which are very similar to those just enumerated. Thus, its removal on one side causes the animal to tilt its head and to move about in a circle toward the injured side. Moreover, when this animal is placed upon its back, it experiences great difficulty in righting itself, and when made to swim, frequently executes rotary movements toward the operated side. Its musculature exhibits a decided loss of tonus and precision of action. Disorders of a very similar kind are exhibited by mammals after the destruction of one or more sets of semicircular canals.

The Effects of Stimulation of the Semicircular Canals.—Ewald¹ has succeeded in rendering certain canals functionally useless by opening their bony wall with a dentist's burr and temporarily compressing their membranous tube by means of a plug of amalgam, but the disorders in the plane of this particular canal were evinced only after the corresponding membranous tube on the opposite had also

¹ *Physiol. Untersuchungen über das Endorgan des Nervus octavus*, Wiesbaden, 1892; also: *Schrader, Pflüger's Archiv*, xli, 1893, 75.

been blocked. König and Brener¹ have obtained very similar results by painting the ampulla with cocain so as to paralyze the nerve-endings. These data serve to contradict the view sometimes advocated, that the disorders following lesions of the semicircular canals, are phenomena of stimulation rather than of abolition of function (Ausfallserscheinungen). Besides, of course, we are in possession of the fact that these disorders are generally lasting in character.² Ewald has also stimulated the membranous canal by pressing upon it with a bristle inserted through an opening in the bony canal, and by blowing a current of air upon it through a narrow tube. In another set of experiments the endolymph was made to circulate by this means first in one direction and then in the other. In the dog-fish, Lee³ has found that pressure upon any particular ampulla gives rise to movements of those fins which this animal ordinarily employs in moving in the plane of the canal stimulated. Electrical stimulation of the canals has been resorted to by Brener. It gives rise to the so-called galvanotropic reaction, consisting in a deviation of the head toward the anode. All these procedures have fully confirmed the theory of Brener and Mach which holds that the specific stimulant of the sensory epithelium of the ampulla is the movement of the endolymph. Besides, it has been made evident that these canals evoke movements only along particular planes of the body.

Labyrinthine Reflexes and Tonus.—The sensations of movement with which we are concerned at the present time are, of course, passive in their nature and enable us to form judgments regarding movements along straight and curved lines. These purely labyrinthine impressions, however, are supplemented by others received from the retinae, the cutaneous receptors, and the proprioceptors proper. It cannot surprise us, therefore, to find that this relationship is sometimes reversed, so that the labyrinthine sensations become associated with compensatory reactions of different kinds. Chief among these are movements of the eyes and head. If a frog is placed upon a board and is slightly moved around its transverse axis, it raises and lowers its head against the direction of this movement. In a similar way, if rotated upon a horizontal disc, it bends its body against the direction of the rotation. These compensatory reactions cease immediately if the labyrinth is destroyed or if the nerve fibers leading from it are cut. Equally pronounced effects may be obtained in the fish,⁴ birds and mammals. Since these compensatory movements may also be evoked in the blind and are, therefore, entirely independent of visual sensations, their labyrinthine origin cannot be doubted.

As has been pointed out by Purkinje, Ewald and Stein,⁵ any

¹ Sitzungsber., Akad. zu Wien, cxii, 1887, 1903.

² Gaglio, Archiv ital. de biologie, xxxi, 1899, 377.

³ Jour. of Physiol., xvii, 1895, 192.

⁴ Loeb, Pflüger's Archiv, xlix, 1891, 175.

⁵ Zentralbl. für Physiol., xiv, 1900, 222.

unusual rotation, say, around the longitudinal axis of the body, gives rise to a horizontal nystagmus of the eyes. This phenomenon consists in a slow lateral movement of the eyes in the plane of the rotation which, however, is soon stopped and superseded by an abrupt return of the eyes into the midline. This rotation-nystagmus is to be sharply differentiated from that form of nystagmus which is frequently exhibited by persons looking out of the window of a railway car. The former occurs even in the dark and in blind persons, while the latter does not, and may be suppressed by fixedly gazing into space. A nystagmus of the entire head is often observed in birds when made to stand upon a rotating surface. The head is at first turned against the direction of the rotation and is then made to execute jerky movements around the long axis of the body.

Compensatory movements of the entire body are frequently noticed after rather excessive rotation. Thus, if we turn around the longitudinal axis of our body a number of times and then suddenly stop, it will be found that the objects in space continue to move against the direction of the rotation, while we ourselves leave our previous position and sway toward the rotation. It is to be noted, however, that this compensation is forced upon us reflexly and should not be mistaken for the ordinary effects of the momentum of the rotation. In addition, it is easily observed that these compensatory movements are confined chiefly to the head and trunk and would, in the absence of corresponding movements of the legs and arms, give rise to a complete loss of equilibrium.

These rotation experiments should be executed with some caution, because in hypersensitive persons they are prone to produce nausea, vomiting, muscular weakness, disturbances in vision and slight cardio-inhibitory effects. For this reason, it is commonly held that seasickness is caused by an unusual and excessive stimulation of the static and dynamic sense-organs. A similar complex of symptoms, aggravated, however, by vertigo, forced movements and a constant ringing in the ears, is presented by Menière's disease.¹ The latter seems to have its origin in an inflammatory and hemorrhagic affection of the semicircular canals and neighboring nerve fibers. It is also well recognized that the injection of solutions into the tympanic cavity as a curative means in affections of the middle ear may give rise to vertigo and nystagmus; in fact, in some persons, loud noises suffice to induce these symptoms.

The character of the results obtained with deaf persons, differs with the extent of the lesion. Inasmuch as only about 65 per cent. of these persons show a lesion of the canals in addition to that of the cochlea, it cannot surprise us to find that many of them present absolutely no disorders of their senses of position and movement. The others have learned in the course of time to compensate for the disturbances

¹Gaz. méd. de Paris, 1861; also: Frankl-Hochwart, *Das Menièr'sche Symptomen-complex*, Wien, 1906.

in these sensations and behave normally unless subjected to unusual conditions. Thus, the tests of James¹ have proved 186 among 500 deaf persons to be without vertigo when rotated, and 15 among 25 deaf persons to lose their sense of orientation while diving. Normal persons, of course, behave very differently; 199 of the 200 examined displayed vertigo and forced movements.

The general weakness of the musculature following injuries to the labyrinth, is attributed by Ewald to a loss of the labyrinthine tonus, mediated by a set of impulses which reflexly keep the musculature in a state of alertness. This effect is obtained through the intervention of the cerebellum with which the labyrinth is in close functional relation. Thus, we find that the vestibular fibers of the auditory nerve terminate in the nucleus of Deiters and the nucleus of Bechterew, where reflex connections are formed with the cranial nerves and the different motor centers. Connections are also established here with the nucleus fastigius and the cortex of cerebellum. The semicircular canals, therefore, serve as a sense-organ of the cerebellum, this central structure enabling the sensations derived from them, to influence the tonus and behavior of the musculature and hence, also muscular coördination and the equilibrium.

The Activation of the Hair-cells of the Ampulla.—The first definite explanation of the action of this receptor has been given by Goltz² who assumed that the endolymph of these canals rests upon the sensory epithelium with a certain pressure and that this pressure changes with the position of the head. But, while he regards them very distinctly as organs of equilibration, he seems to believe that they are activated solely by hydrostatic differences. This principle has been more fully developed by Brener,³ but this investigator abandons the hydrostatic factor or gravitation almost altogether and puts in its place a hydrodynamic mechanism. This amplified theory which has been materially strengthened by a number of observations made by Mach and Brown,⁴ brings forth the conception that the hair-cells constitute the peripheral elements of equilibrium, and that their activation is accomplished by the changes in the pressure which the endolymph must suffer whenever the canals are moved. Thus, it is assumed that the different movements of the head give rise to oscillations of the endolymph which in turn affect the position of the hair-like processes of the ampullar lining cells. To be sure, the simple effects of gravity cannot be excluded altogether, but this theory subordinates the latter completely to those of movement.

If a tumbler is filled with water and is twirled upon a rotating disc, it will be noted that its walls move first, while the water lags behind, and exerts a pressure in the opposite direction. If the twirling is

¹ Amer. Jour. of Otology, 1887; also: Kreidl, Pflüger's Archiv, li, 1892, 119.

² Pflüger's Archiv, xxx, 1870, 172.

³ Sitzungsb. der Akad. zu Wien, cxii, 1903.

⁴ Jour. of Anat. and Physiol., viii, 1874, 327.

continued for a brief period of time, a point will be reached when the walls and the water move with practically the same velocity. Im-

FIG. 402.—DIAGRAMMATIC REPRESENTATION OF A MODEL ILLUSTRATING THE DEVIATION OF THE HAIR PROCESSES OF THE AMPULLA.

D, disc rotated by hand; *T*, circular glass tube filled with water; *B*, bulbular enlargement containing a long camel's hair brush, vertically placed.

mediately upon ceasing the rotation, the walls are brought to a standstill, while the water continues to move in this direction until it is finally stopped by the friction. These

FIG. 403.—DIAGRAM ILLUSTRATING THE POSITION OF THE HAIR PROCESSES OF THE AMPULLA ON ROTATION OF THE CANAL.

A, the canal being moved in the direction of the black arrow, the endolymph at first lags behind. The hairs processes are deviated against the rotation from *a* to *b*. On stopping the rotation of the canal, the endolymph is carried onward in the direction of the red arrow deviating the hair processes from *a* to *c*.

phenomena may be illustrated in a more striking manner with the help of a circular glass tube filled with water and enlarged at one point for the reception of a bundle of soft hairs placed transversely into its lumen (Fig. 402). When rotated, this primary and secondary dissociation between the movements of the walls of the tube and the water are now made more evident by the deviation of the hairs, first against and then in the direction of the rotation.

If this hydrodynamical principle is applied to the semicircular canals, it must be concluded that the movement of the head gives rise to a movement of the canals situated in this particular plane. To begin with, the endolymph lags behind the walls of the canals, but soon attains the same speed as the latter. Lastly, it continues in this direction even after the canals have ceased to move until its motion has again been arrested. This implies that the hair processes are first turned against the rotation, then vertically into the fluid, and lastly

turned against the rotation, then vertically into the fluid, and lastly

in the direction of the rotation. These progressive deviations of the hairs evoke those sensations which inform us regarding the direction and extent of the movement executed by us. It should be emphasized, however, that the endolymph does not move about in a circle through the entire canal, but undergoes simply the slightest possible oscillations in the manner just indicated with the help of the preceding schema. This must necessarily be so, because (a) the internal diameter of the semicircular canals of man measures only 0.1 mm. (0.04 mm. in the pigeon), (b) because their course is not absolutely circular, and (c) because the endolymph possesses a relatively high viscosity.

Naturally, only those hair cells can be affected by a certain general movement which lie in this particular plane. It has previously been mentioned that the semicircular canals act in pairs, *i.e.*, the anterior of one side is stimulated simultaneously with the posterior of the opposite side. Both together control movements along vertical planes. The horizontal canals also act in unison, but are chiefly concerned with movements along the horizontal plane. Intermediate movements always stimulate two adjoining pairs of canals but in an unequal degree. There is this to be remembered, however, that the primary sensation arises at the beginning, when the movement of the canal is toward the ampulla and hence, when the pressure of the endolymph is exerted in the direction from the utricle toward the other extremity of the canal. Psychically, therefore, all movements are interpreted correctly, although in a manner opposite to the position of the hair-like processes. The secondary dynamic effect, producing the deviation of the hairs at the end of the rotation, does not stimulate unless excessive. In the latter case, a sensation of rotation is produced in a direction opposite to the primary.

Naturally, the labyrinthine sensations of movement are augmented by others to form the sense of equilibrium. Chief among these are the sensations of position, the muscle-sense and the sensations of sight and touch. Ewald believes that all these unite in regulating the tonus of the musculature which forms the basis of the stability of our body. If the body sways toward one side, the stimulation of the hair cells then ensuing, gives rise to an increase in the tonus of the muscles ordinarily counteracting this movement. In this way, the labyrinthine reflexes are utilized, together with others, in evoking those compensatory reactions which are directly responsible for our orientation in space. This point has found substantiation in the experiments of Magnus and Klijn,¹ made upon cats during the condition of decerebrate rigidity. The muscles of the extremities having been rendered rigid by the removal of the cerebrum, the mere tilting of the head of the animal sufficed to produce perfectly definite changes in the position of its limbs. Besides, these compensatory reactions disappeared immediately after the destruction of both labyrinths.

¹ Pflüger's Archiv, cxlv, 1912, 455.

SECTION XXIII

THE SENSE OF SIGHT

CHAPTER LXVII

PHYSIOLOGICAL OPTICS

The Nature, Cause and Velocity of Light.—The study of the phenomena connected with light, and their application, is called optics. Physiological optics is that subdivision of optics which deals with these phenomena as applied in a practical way to our visual mechanism. In accordance with Aristotle, the universe consists of four mundane elements, earth, fire, water, air and a fifth submundane, or ether. This name was applied to this element on account of its ethereal circular movement and not on account of its "fire." At the present time, of course, we are concerned solely with those ethereal impacts which give rise to illumination, and particularly with those which affect the retinæ of our eyes, because, as commonly understood, light is that form of energy which by its action upon this receptor, evokes the phenomenon of vision. In this group must be placed the ethereal vibrations forming the spectral colors, namely, vibrations possessing a rate per second of 482,000,000,000,000 for red light and of 707,000,000,000,000 for violet light.

The different sources of light may be divided into natural and artificial. The most important among the former is the sun. Then follow the fixed stars, nebulae, comets, meteors, lightning, auroras and lights modified by reflection and refraction, such as that of the rainbow, clouds, and phosphorescent and fluorescent bodies. Among the artificial sources might be mentioned the combustions of gas, oil, wood, coal, etc., and the illumination produced by the electric current and mechanical impacts. But, since we are dealing in the latter case with certain forms of stored energy, all these sources of light must have had originally an exherent cause, presumably the sun.

Regarding the cause of light two theories have been propounded, namely, the *emission or corpuscular theory*, generally accredited to Newton, and the *undulatory theory* of Huyghens and Euler. The first assumes that the different luminous bodies actually discharge certain particles or molecules in straight lines. Consequently, luminous vibrations are really transverse in their direction, while those of sound are longitudinal. This assumption would lead us to infer that the retina is stimulated by actual molecules of matter. The second theory holds that all space is filled with an attenuated medium, called luminiferous ether, which is set into rapid vibration. This conception would imply that the retina is stimulated by the vibration of the molecules of the ether, in analogy with the excitation of the organ of Corti by vibrations or waves occurring in the ordinary atmosphere.

These vibrations in ether are propagated at an almost inconceivably rapid rate. If we reckon the distance of the earth from the sun at 91,500,000 miles, the speed of sunlight may be calculated at 185,500 miles in a second. Thus, it would require this light about eight minutes to reach the earth, that of Neptune about four hours, that of Centaurus close to 4 years and that of Sirius 17 years. Light therefore, travels with a velocity which is 900,000 times greater than that of sound; moreover, its stimulating power is extremely great, because a flash of lightning, lasting $\frac{1}{1,000,000}$ sec., suffices to produce a visual sensation. Sunlight, of course, is the strongest light, equalling the power of 5500 candles placed at a distance of one foot. It is 600,000 as strong as the reflected light of the moon and 16,000,000,000 as strong as that of Centaurus.

In passing away from its source, light is brought into contact with different bodies, which tend to hinder its course. Only the most perfect vacuum allows it to pass with as much freedom as the air. Other media are classified as transparent, translucent and opaque. *Transparent media* permit of the passage of white light, as well as of its spectral components, so that any object may be seen through them in its different colors. Among these might be mentioned the air, water, glass, the humors of the eye, and others. *Translucent bodies* allow only a certain number of the light rays to pass, so that a clear outline of the objects cannot be obtained. *Opaque bodies* cannot give rise to visual sensations, because they prevent the passage of these rays, although permeable to them. The light is then said to be absorbed, *i.e.*, it is converted into some other form of energy, such as heat.

Reflection.—Luminous bodies are those which emit light, such as the sun or substances when undergoing combustion. A luminous ray, therefore, may be defined as the direction of the line in which light is propagated, and a pencil of light as a collection of rays from the same source. In this form, it consists of a number of divergent rays, *i.e.*, of rays which in passing away from the luminous object, gradually become more widely separated from one another. A beam of light includes a large number of light rays showing measurable dimensions. It embraces divergent, parallel and convergent rays, but the convergent rays are of no use to us under ordinary conditions.

If light is made to pass through a homogeneous medium, such as air, glass or water, it is propagated onward in a right line, while if an opaque body is placed in its path, it will be intercepted by it and be absorbed or reverberated. In the latter case, the light is forced to change its direction, although allowed to continue onward in the same medium. To this phenomenon the name of reflection has been given. Reflecting bodies may be polished or unpolished. The first give rise to regular and the second to diffused reflection. Thus, if a beam of light is incident upon a well-polished mirror, the greater part of the light is reflected in a single direction at a perfectly definite angle; in fact, the reflection is so precise that it may be said to be governed by two laws, as follows:

(1) The reflected ray *BE* is in the plane of the incident ray *DB* and a normal or perpendicular *AB* erected upon the reflecting surface *CF* at the point of incidence *B* of the ray (Fig. 404).

(2) The angle *EBA* formed by the reflected ray and the perpendicular, equals the angle *DBA* made by the incident ray and the perpendicular. In other words, the angle of reflection is equal to the angle of incidence.

A beam of light falling upon an unpolished surface suffers a reflection of its rays in all directions, because inasmuch as the surface is composed of projecting particles which receive incident rays at all angles, the reflected rays must be diffused or scattered in all directions. Naturally, the intensity of the reflected light is always less than that of the incident light, because at least some of the original vibrations

FIG. 404.—REFLECTION FROM PLANE MIRRORS.

are converted into vibrations of the reflecting surface. Thus, the intensity of the reflected light really depends upon (a) the brilliancy of the source of light, (b) the perfection of the polish, (c) the angle of the incident ray, (d) the character of the reflecting substance, and (e) the character of the medium in which the reflection is taking place.

In accordance with their shape, reflecting surfaces may be classified as plane, concave, convex, spherical, parabolic, conical, etc. The reflection from a *plane mirror* is illustrated by Fig. 404. If a ray of light emitted by point *D*, meets the surface *CF* at the angle *DBA*, the reflected ray forms the angle *EBA*. The eye at *E* then sees the image of *D* as if it were placed at *I*, this point being situated where the prolongation of *EB* intersects the perpendicular drawn through *D*. Hence, the determination of the position and size of images formed by plane mirrors, resolves itself into a determination of the image points of the several different luminous points. It will be seen, therefore, that the image is perceived as being located behind the mirror at a distance equal to that of the given points.

FIG. 405.—REFLECTION FROM A CONCAVE SPHERICAL MIRROR IF ITS INCIDENT RAY IS PARALLEL.

Spherical mirrors are those possessing the curvature of a sphere, and are formed, therefore, by the revolution of an arc around the radius *CD*. The inner *concave* and the outer *convex* surface may of course be supposed to be made up of an infinite number of plane mirrors. Reflection may take place from the former as well as from the latter. *C*, the center of the hollow sphere, constitutes the *geometrical center* or *center of curvature*, while a line drawn through *C* and *D*, forms the

principal axis of this reflecting surface. Any other line passing through C to a different point of the mirror than its middle, constitutes a *secondary axis*. The perpendicular of each of the small planes forming this reflecting surface, is the radius of the sphere and each reflected ray forms with the corresponding radius the same angle as the incident ray. Thus, all rays parallel to the principal axis (AB and EH , Fig. 405) are brought to a focus at the *principal focus* F midway between C and D . Quite similarly, all rays pursuing a course parallel to any secondary axis, are brought to a focus in a point lying on this axis. Hence, if the principal focus F were converted into a luminous point, the rays emitted from here would be reflected back into rays taking their course parallel to the principal axis.

If the luminous point L is situated upon the principal axis at a distance insufficient to render the rays emitted by it parallel, then the divergent incident ray LB (Fig. 406) and the perpendicular BC form the angle LBC . This angle is smaller than that formed by the parallel ray AB with the corresponding normal BC ; and hence, it may be inferred that the angle of reflection of a divergent ray is smaller than the angle of reflection of a parallel ray. Consequently, the principal focus of L must lie in L' between F and C ; i.e., between the center of curvature and the

FIG. 406.—REFLECTION FROM A CONCAVE SPHERICAL MIRROR IF ITS INCIDENT RAY IS DIVERGENT.

principal focus F . By converting L' into a luminous point, the rays may in the same manner be reflected outward into L . The latter, therefore, may be said to be the *conjugate focus* of L' . It will then be seen that if the luminous point L is placed in the center C , the angle of incidence is null and the angle of reflection null. Consequently, the ray is reflected upon itself so that its focal point coincides with the luminous point. Lastly, if the luminous point L is situated between the center of rotation C and the principal focus F , the conjugate focus must be on the other side of the center and the farther from it, the shorter the distance between L and the principal focus. These principles find their application in the explanation of Purkinje's image reflected from the concave anterior surface of the vitreous humor.

The reflection from convex spherical surfaces finds its application in the images formed upon the anterior surfaces of the cornea and lens. Supposing that the entering ray pursues a course parallel to the principal axis of the convex mirror, its reflection from the latter will give to it a divergent course. If the reflected ray is continued by an imaginary line through the mirror, it will be seen to strike the principal focus at F which is approximately the center of the radius of curvature CD of this mirror.

The images formed by rays of light differ with the direction assumed by them after their reflection. When they converge, as after their reflection by concave mirrors, they form a *real image* in front of the mirror and on the same side as the

object. A real image, therefore, is produced by the reflected rays themselves, and may be observed with the aid of a screen properly adjusted at their points of intersection. Divergent rays, on the other hand, are supposed to be projected directly through the mirror and are seen as if they proceeded from its other side. In the latter case, the image has no real existence, but is effected by the prolongations of the reflected rays backward. This is called a *virtual image*. Obviously, therefore, a *real focus* is formed by the reflected rays themselves, while a *virtual focus* is formed by their prolongations backward through the mirror.

Refraction.—If a ray of light is made to pass from one medium into another in a perpendicular direction, it is not deviated from its course. The contrary result, however, is obtained if it is made to enter in an oblique direction. To this phenomenon the term of refraction has been applied. It is to be remembered that not all the rays of a certain beam of light are refracted, because some of them are reflected from the surface in accordance with the character of the medium into which they have been directed. Those that actually enter the denser medium are refracted, because their velocity of propagation is now less than it was in the rarer medium. The degree of refraction differs with the relative densities of the two media. Supposing that we are dealing with air and water separated by a thin

FIG. 407.—DIAGRAM ILLUSTRATING REFRACTION.

FIG. 408.—DIAGRAM ILLUSTRATING REFRACTION.

layer of glass (Fig. 407), it will be found that any ray directed vertically to the surface of the latter (AB), is not deviated from its course (BC). Any incident ray, however, which strikes the surface of the water obliquely (DB), is deflected (BE) toward the perpendicular AC. The angle of incidence ABD is then larger than the angle of refraction CBE, and naturally, this angle becomes the smaller, the greater the refracting power or density of the second medium. The ratio between the angle of incidence and the angle of refraction constitutes the *index of refraction*. When passing in the opposite direction (Fig. 408), namely from a medium of greater into one of lesser density or refractive power, the ray BE is bent away from the perpendicular rendering the angle of refraction greater than the angle of incidence. Thus, taking the index from air to water to be $\frac{4}{3}$ and from air to glass $\frac{3}{2}$, the course of the ray in the opposite direction would show an index of $\frac{3}{4}$ and $\frac{2}{3}$ respectively.

The first law of refraction states that the refracted ray is in the

same plane as the incident ray and the perpendicular drawn to the surface, separating the two media. The second law is that the ratio which the line of the incident ray bears to the line of the angle of refraction, is constant for the same two media but different for different media.¹

Refractive media may be bounded by:

(a) Two plane surfaces which are parallel to one another. A ray impinging upon a *plate* at a right angle, traverses this medium without suffering a change in

FIG. 409.—DIAGRAM ILLUSTRATING REFRACTION BY A PLATE-LIKE BODY.

FIG. 410.—DIAGRAM ILLUSTRATING REFRACTION BY PRISMS.

its direction. Any other ray DB meeting this surface at an angle, is bent toward the perpendicular AB on entering, but away from it on leaving the medium. The emergent ray EF is parallel to the incident ray (Fig. 409).

(b) Two plane surfaces which incline toward one another. At the point of intersection of these two surfaces is the summit or apex A . Their inclination constitutes the refractive angle and their right line BC the base. The medium so outlined is a *prism* (Fig. 410). A ray of light LE impinging upon one of its lateral surfaces AB , is deflected toward the normal P at E , because it passes into a more highly refractive medium. It here forms the angle of incidence LEB and the angle

FIG. 411.—DIFFERENT FORMS OF CONVEX AND CONCAVE LENSES.

of refraction IEF . When meeting with the other surface AC it is again refracted, the angle of refraction HFK being greater than the angle of incidence EFI ; because it passes from a more highly refractive medium into one of less power. Thus, the ray is deflected from its course in the direction of the base of the prism. In this case, the image of L is produced at S , in the prolongation of the emerging ray.

(c) Two surfaces one of which is either curved or plane. The refractive medium is thus arranged in the form of a *lens* which in accordance with its shape may be spherical, cylindrical, elliptical or parabolic. In optics spherical lenses are most commonly employed and they may be made of crown glass or flint glass. The former is free from lead and is therefore less refractive than the latter which contains lead. By combining spherical surfaces either with plane or curved surfaces, six

¹ Stated by Snell in 1620, but enunciated by Descartes.

different kinds of lenses are obtained, namely (a) plano-convex, (b) biconvex, (c) concavo-convex, (d) plano-concave, (e) biconcave and (f) concavo-convex (Fig. 411). The lens in our eye is a double convex or biconvex lens, but we shall have occasion to refer to the other types of lenses, as well as to prisms and planes when discussing errors in refraction and their correction.

Refraction by a Biconvex Lens.—A biconvex lens is essentially the segment formed at the intersection of two spheres drawn upon the same line with either the same or different radii (Fig. 412). Hence,

FIG. 412.

FIG. 413.

FIG. 412.—DIAGRAM ILLUSTRATING THE FORMATION OF BICONVEX LENS.

FIG. 413.—STRUCTURE OF BICONVEX LENS. (From Draper "Medical Physics.")

a line prolonged through the centers of curvature of the two surfaces of this lens (AB), must form the *principal axis* of this system. Between these two centers lies a point C which possesses the property of permitting rays to pass without refraction, so that the emergent ray is parallel to the incident ray. This point constitutes the *optical center* of the lens. Any other line passing through this center is a *secondary axis*.

The action of a biconvex lens upon the entering rays of light is easily understood if the lens is imagined to be composed of a number of prisms arranged in the manner

FIG. 414.—CONVEX LENS DISSECTED. (From Draper "Medical Physics.")

indicated in Fig. 413. It will be remembered that a prism deflects or deviates the ray toward its base; hence, a biconvex lens deflects the entering rays in accordance with the refractive power of its prismatic constituents. Inasmuch as the central prisms d , e , etc., have a smaller refracting angle than the outer one f and g , they must give rise to a lesser deviation. The same holds true of the prismatic elements situated above the principal axis, and whether in the vertical, horizontal or oblique meridian of this lens. Their tips are of course directed outward and their bases inward; and furthermore, the central ray following the line of the principal axis, is not deflected at all. It will be seen, therefore, that a biconvex lens possessing

properly centered prisms, converges the previously divergent rays, so that luminous point A is brought to a precise focus in C upon the principal axis.

In ascertaining the formation of an image by a double convex lens, it must be remembered that all objects possess numerous luminous points, the rays emitted by them being collected by the lens into a corresponding number of foci. This implies that under ordinary conditions, the image furnished by a biconvex lens, is real. Supposing that we are dealing with a biconvex lens of the refractive power of the lens of our eye, and place an object in front of it at a distance of more than twenty feet, then the object emits, among others, a large number of rays which pursue a course parallel to the principal axis of this lens (AB etc., Fig. 415). All these rays are converged to very nearly the same focus F upon the principal axis. The dis-

FIG. 415.—DIAGRAM ILLUSTRATING THE REFRACTION OF PARALLEL RAYS BY A BICONVEX LENS.

tance LF , is known as the *principal focal distance*. If the object is now moved farther away from the lens, the *principal focus* F moves toward the lens, while if the object is placed nearer the lens but not close enough to render the rays divergent, the focal point F moves farther backward. Lastly, if F itself is rendered luminous, the rays emitted from here traverse the lens in the opposite direction and leave its anterior surface parallel to the principal axis. This is merely a reversal of the previous condition in which parallel rays are brought to a focus in F .

If a luminous point L is placed upon the principal axis at a distance greater than the focal distance of this lens, but not far enough from it to cause its rays to become parallel, then the rays diverging from it are brought to focus in L^1 , at a

FIG. 416.—DIAGRAM ILLUSTRATING THE REFRACTION OF DIVERGENT RAYS BY A BICONVEX LENS.

point beyond the principal focus F (Fig. 416). In case L^1 is now rendered luminous, its rays are brought to a focus in L . For this reason, these points are commonly spoken of as *conjugate foci*. By moving luminous point L nearer to and farther away from the lens, the focal point L^1 may be made to move first farther away and then nearer to the lens. In the first case, a point will be reached when the emerging rays finally become so greatly divergent that they cannot be focalized at all (Fig. 417). This effect appears whenever the luminous point L is situated nearer the lens than its principal focal distance. In this case, a virtual focus is formed at L^1 , at the intersection of the prolongations of the emerging rays.

If rays are directed into this lens which are already convergent, their convergence is simply increased so that their focal point comes to lie nearer the lens than

it would if the rays entering it had been parallel. This is the function of the cornea. It tends to gather the slightly divergent rays and to render them available for refraction by the lens. This discussion shows that if an object, even a very large one, is placed at a sufficient distance from a biconvex lens, a small real and inverted image of it is formed just outside the principal focus F . The greater the

FIG. 417.—DIAGRAM ILLUSTRATING THE REFRACTION OF EXTREMELY DIVERGENT RAYS BY A BICONVEX LENS

distance, the smaller this image. This principle is illustrated by our eye as well as by the ordinary photographic camera. Quite similarly, one small object placed upright just outside the principal focal point F of a biconvex lens, forms a large inverted image at a considerable distance in front of the lens. This principle is illustrated by the projection lantern.

FIG. 418.—DIAGRAM ILLUSTRATING FORMATION OF AN IMAGE BY A BICONVEX LENS.

In constructing the image of an object AB as formed by a biconvex lens, it must be remembered that one ray AD emitted by luminous point A , always traverses the nodal point of the lens N unrefracted and that a second ray AE enters the lens parallel to its principal axis (Fig. 418). The ray AE is then refracted through the focal point F . The focal point of A lies at the point of intersection of these two lines.

FIG. 419.—DIAGRAM ILLUSTRATING THE REFRACTION BY A BICONCAVE LENS.

If this construction is now extended to a luminous point B upon the lower end of the object AB , it will be seen that this one is brought to a focus above. Consequently, the image of object AB is inverted. In those cases in which the object is placed between the biconvex lens and its principal focus, only virtual erect images are formed. This principle is made use of in the construction of microscopes and magnifying glasses.

Refraction by a Biconcave Lens.—To understand the refraction by biconcave lenses, imagine the lens to be composed of a number of prisms, which in cross-section have their apices directed toward the center or axis of the lens and their bases toward the periphery. If we remember that the rays entering the inclination of a prism, are deflected toward its base, it must be evident that a biconcave lens renders the rays divergent (Fig. 419). Like the concave mirrors, these lenses give rise to virtual images. When the incident ray meets the anterior surface of this lens, it is refracted toward the perpendicular, *CB*, but away from it at *H*. This double refraction also takes place with every other ray, for example, with *DE* and hence, there is no real focus established. The prolongations of these rays intersect in *F* which is the principal virtual focus.

CHAPTER LXVIII

THE GLOBE OF THE EYE AND ITS PROTECTIVE APPENDAGES

The General Structure of the Eyeball.—The eyeball is placed in the fore part of the orbital cavity and is adjusted in such a way that it may be activated by almost any ray projected toward it. Its range is greatly increased by the fact that it may be moved in different directions by means of muscles attached to its external coat. In the mammals, the visual mechanism consists of two eyeballs and their connections with the centers for vision in the occipital cortex of the cerebrum. This implies that these animals are in possession not only of a most highly developed receptor, but also of the means of forming the best possible concepts. In this regard they are sharply differentiated from the lower forms which, although equipped with receptors of sufficient sensitiveness toward the ethereal impacts, are quite unable to associate them properly, because they lack the central organ essential for this function. Many of the lower forms are able to perceive light by means of their pigment spots and other cutaneous sense-organs,¹ but react toward it merely in a reflex way, by displaying phenomena similar to the heliotropism or phototaxis of the lowest organisms. In a way, these forms are really in the same position as we would be if our eyelids were kept permanently closed, because although still able to appreciate differences in the intensity of the illumination, we would then react in accordance with these and no longer depend upon distinct visual impressions and concepts.

A much more advanced state of development is attained by the eye of the higher invertebrates. That of the insects is composed of

¹ Hesse, *Das Sehen der niederen Tiere*, Jena, 1908.

numerous funnel-shaped tubules, through which the rays of light are refracted by means of a lens-like structure of chitin. This type of eye, however, is soon abandoned, because already in the cephalopods we find a single system of curved refracting media. In the vertebrates the eye is constructed along very similar lines. Retrogressive it becomes in proteus and sphalax, because these animals live permanently in the dark.

The eye is the organ of space, its purpose being to form images of external objects upon the retina which are then conveyed into consciousness. Its general structure and manner of action reminds

FIG. 420.—DIAGRAM OF A HORIZONTAL SECTION THROUGH THE HUMAN EYE.

C, cornea; *A*, anterior cavity; *P*, posterior cavity; *L*, lens; *J*, iris; *T*, conjunctival sac; *CL*, ciliary ligament; *CB*, ciliary body; *CM*, ciliary muscle; *OS*, ora serrata; *CS*, canal of Schlemm; *R*, retina; *Ch*, choroid; *S*, sclera; *ON*, optic nerve; *A*, retinal artery; *B*, blind spot; *Y*, yellow spot; *OA*, optical axis; *VA*, visual axis; *H*, hyaloid canal.

us of the camera obscura, the box of which is represented by the corneal and sclerotic envelope of the eyeball, its refracting medium by the aqueous humor, lens and vitreous humor, its diaphragm by the iris, and its sensitive screen by the retina. Its most essential constituent is, of course, the retina, while its other structures merely serve the purpose of adjuncts to effect a proper concentration of the rays of light.

The eyeball is spheroid in shape and is loosely held in the orbital cavity by a fibrous membrane, known as the capsule of Tenon. Its anteroposterior diameter measures about 24 mm., and its transverse and vertical diameters about 22 mm. In longitudinal section it is seen to be composed of the segments of two spheres, of which the pos-

terior occupies five-sixths and the anterior one-sixth of the entire spheroid. At about the line of junction of these segments is placed a partition consisting of the ciliary body, iris and lens. In this way, the cavity of the eyeball is subdivided into two, known respectively as the anterior and posterior cavities. The former is filled with aqueous humor and the latter with vitreous humor. It is also to be noted that the wall enclosing the former is in part translucent (cornea), whereas that of the latter is opaque.

The Minute Structure of the Eyeball.—The shell of the eyeball consists of three layers arranged concentrically as an external, a middle and an internal coat. The outermost or *sclera* is made up of dense, tough, opaque fibrous tissue which is interwoven with elastic fibers and is distributed longitudinally and transversely around the eyeball. If the eyelids are widely separated, its anterior zone appears as the “white of the eye.” In children it has a bluish color, owing to the fact that it is not sufficiently thick to prevent the dark choroidal pigment from showing through. It is thickest posteriorly (1.0 mm.) at the entrance of the optic nerve, and thinnest (0.4 mm.) about 6 mm. from the cornea. Anterior to this point it is again thickened to give attachment to the tendons of the recti muscles. The optic nerve and the retinal blood-vessels pierce the sclera about 2.5 to 3 mm. internal to the posterior pole of the eyeball and about 1 mm. below the horizontal line uniting its anterior and posterior poles. By virtue of its firmness, the sclera serves to retain the shape of the eyeball and to protect its soft internal structures. In this it is aided by the fact that the humors of the eye are held under a certain pressure which is designated as the intraocular pressure.

The *cornea* which is really the modified anterior segment of the sclerotic coat, is transparent and allows the rays of light to enter the interior of the eye. Looked at from in front, it possesses a nearly circular outline, measuring about 12 mm. in its transverse and 11 mm. in its vertical diameter. In infants, its central zone is generally somewhat thicker than its marginal, while in the adult it is somewhat thinner¹ (0.45 to 1.37 mm.). Its curvature is less than that of the sclerotic, but varies in different persons as well as at different periods of their life; moreover, its curvature is generally greater in its vertical than in its horizontal meridian.

The substance of the cornea is made up of modified connective tissue which is continuous with that forming the sclera. Its anterior surface is enveloped by stratified epithelium which is supported by a structureless membrane, known as the anterior homogeneous lamella. Its posterior aspect is covered by a simple layer of endothelial cells situated upon the posterior homogeneous lamella. The latter is a very resistant membrane, as may be gathered from the fact that it serves as a barrier to inflammatory processes. In addition, it prevents the absorption of the aqueous humor through the corneal lymphatic spaces. Close to the margin of the cornea, this membrane breaks up into a number of interconnected lamellæ which either serve as attachments to the ciliary muscle or are prolonged backward into the substance of the iris and sclera. The fissures in between these lamellæ are known as the spaces of Fontana. They communicate freely with the anterior cavity of the eye as well as with the canal of Schlemm, a circular tube traversing the substance of the sclera, close to its junction with the cornea. The latter is

¹ Blix, Monatsblatt für Augenheilkunde, 1872.

generally regarded as a sinus-like vein which serves as a drainage tube for the aqueous humor.¹

The cornea is not provided with blood-vessels, excepting along its margin, where the conjunctival and sclerotic capillaries form superficial and deep networks. Furthermore, since this structure is also devoid of lymphatics, its nutrition must be effected by the lymph contained in its connective-tissue spaces. It need scarcely be emphasized that this arrangement is of great functional importance, because it enables the rays of light to gain the pupillar aperture without being unduly deflected from their course. The nerve fibers of the cornea are derived from the plexus annularis surrounding its margin.² From here these fibers strive radially into its fibrous substance, where they form secondary plexuses in the anterior and posterior laminated structures. The fibers of these inner networks are non-medullated.

The *choroid* is in firm contact with the internal surface of the sclera. It is dark brown in color and extends forward to a point very near the cornea where it terminates in the iris. The latter appears as a transverse fold which is attached to the eyeball at its circumference, but is otherwise freely suspended in the aqueous humor in front of the lens. It will be seen, therefore, that this membranous partition divides the anterior cavity of the eyeball into two compartments, called respectively the anterior and posterior chambers of the eye. The former is bounded by the cornea and anterior surfaces of the iris and lens, and the latter by the posterior surface of the iris and anterior surface of the lens. Directly behind the iris, the choroid is folded a number of times into a circular thickening which extends into the anterior part of the vitreous humor. This structure is known as the ciliary body and contains the ciliary muscle. Its inner pole gives attachment to the ciliary ligaments which extend from here to the capsule of the lens. The function of these minute parts will be more fully discussed later on when studying the process of accommodation. The choroid consists chiefly of an extensive ramification of blood-vessels held in place by delicate strands of connective tissue. These vessels are principally derived from the ophthalmic artery and pierce the sclera externally to the entrance of the optic nerve. They are known as the short posterior ciliary, the long posterior ciliary, and the anterior ciliary arteries.

The *retina*, forming the innermost coat of the eye, extends forward to almost the ciliary body. It terminates in this region in a dentated border, known as the *ora serrata*. Externally, its hexagonal pigmented cells lie in close contact with the choroid; in fact, since these cells most generally remain adherent to the latter, when the retina is peeled off, they are commonly regarded as a constituent of the middle coat. It will be shown later on, however, that they are more intimately related to the retina and should, therefore, be considered as a part of this membrane. The thickness of the retina diminishes gradually from behind forward, measuring 0.4 mm. at the yellow spot and 0.1 mm. at the *ora serrata*. When in a perfectly fresh condition, it exhibits a pink color and appears translucent against the hyaline external investment of the vitreous humor. Its blood-supply is derived from the *arteria centralis retinae*, a branch of the ophthalmic which enters the eyeball together with the fibers of the optic nerve, and then subdivides in a radial manner until its terminals reach the *ora serrata*. The microscopic structure of the retina will be more fully discussed later on in connection with its function.

The Eyelids.—The closure of the eyelids is effected (a) volitionally at irregular intervals, (b) involuntarily at rather regular intervals, (c) reflexly in consequence of the excitation of the trigeminus terminals innervating the structures in the vicinity of the eyeball, (d) reflexly on account of the stimulation of the optic nerve by high intensities of light, and (e) during states of cerebral depression and sleep. The mus-

¹ Dogiel, Anat. Anzeiger, 1890.

² Leber and Gidzecker, Archiv für Ophthalm., lxiv, 1906.

cle involved in this process, is the orbicularis palpebrarum which derives its innervation from the facial nerve. The closure of the upper lid is, of course, greatly facilitated by gravity. The opening of the eyelids is effected by the *musc. levator palpebrarum* which raises the upper lid, while the lower lid is carried downward by gravity. The latter may be depressed still further by the contraction of the *musc. rectus inferior*, because the tendon of this muscle and the inferior tarsus are connected with one another by strands of connective tissue. This extra depression, however, is only made necessary when objects in the lower visual fields are to be observed while the head is held erect.

In many fish, amphibia and reptilia, the eye is completely covered by a transparent skin, while others, such as the sharks, crocodiles and birds, are in possession of a third lid which moves transversely across the cornea from its inner angle. This so-called nictitating membrane is represented in the mammals by the *plica semilunaris*. In either case, the eyelids serve primarily as a mechanism of protection against high intensities of light and impacts of different kinds. Under ordinary circumstances, their edges are separated by a cleft measuring about 28 mm. in height. The intervening space is known as the *rima palpebraris*. Inasmuch as the size of the eyeball does not vary very considerably in different individuals, the fact that an eye appears either large or small, is chiefly dependent upon variations in the height of this cleft.

The Lacrimal Glands and Their Secretion.—The internal surfaces of the eyelids are lined with mucous membrane, which is reflected upon the anterior aspect of the eyeball. This lining is known as the conjunctiva and the space between its layers as the conjunctival sac. The latter is, of course, chiefly potential, because the lids are firmly applied to the eyeball and their surfaces are moistened with the secretion of the lacrimal gland. This gland presents a compound tubuloracemose character, and resembles the serous salivary glands.¹ The cytoplasm of these cells contains two kinds of elements, namely, small dark granules and large, clear, vacuolar formations which greatly increase in number during their resting period. If, on the other hand, the secretory nerve of this gland is stimulated or if lacrimation is evoked by means of pilocarpin, these clear bodies disappear, while the dark granules increase in number. The nerve-fibers innervating this gland, are derived from two sources, namely, from the lacrimal branch of the ophthalmic (facial) and from the sympathetic.²

This gland occupies the upper and outer extent of the orbital cavity, while its lower surface rests upon the convexity of the eyeball. Consequently, its secretion is poured into the outer and upper recess of the conjunctival sac, whence it is spread by capillarity across the cornea, moistening its surface as well as that of the opposing conjunc-

¹ Noll, *Archiv für mikr. Anatomie*, lviii, 1901, also: Dobrenil, *Dissertation*, Lyons, 1907.

² Dogiel, *Archiv für mikr. Anatomie*, xlv, 1895.

tiva. Eventually it is collected in the lacrimal lake, a bay-like expansion at the inner angle of the eye overlying the plica semilunaris and the spongy reddish elevation, known as the caruncula lacrymalis.¹ We observe here that each lid is slightly raised into a papilla, the

FIG. 421.—DIAGRAMMATIC REPRESENTATION OF ALVEOLI OF THE LACRIMAL GLAND.
A, during rest; B, after activity produced by pilocarpin.

apex of which displays the orifice (punctum) of a small canal, known as the canaliculus lacrymalis. The purpose of these tubules is to convey the tears out of the conjunctival sac into the lacrimal sac, representing the slightly dilated orbital end of the lacrimal duct.

FIG. 422.—SECTION SHOWING THE COURSE AND RELATIONS OF THE NASAL SAC AND DUCT.
(Slightly modified from Merkel.)

The latter is about 5 mm. wide and 15 mm. long, and continues onward in the form of the nasal duct which finally terminates in the fore-part of the lower meatus of the nose about 30 to 35 mm. behind the posterior margin of the anterior nasal opening (Fig. 422).

¹ Stieda, *Archiv für mikr. Anatomie*, xxxvi, 1890.

These channels are lined with columnar epithelium which becomes ciliated in places. Their walls are strengthened by muscle tissue which on contraction tends to enlarge their lumen. This is especially true of Horner's muscle which envelops the posterior wall of the lacrimal sac and which, during the closure of the lids, widens this passage and aspirates the tears through the dilated punctum. Conversely, the opening of the lids tends to compress the lacrimal sac so that its contents are forced onward into the nasal duct.¹ At this time the sphincter-like punctum is closed, while the valve of Hasner guarding the orifice of the nasal duct, is opened. It should also be mentioned that the tears are ordinarily prevented from escaping across the edges of the eyelids by the oily deposits furnished by the Meibomian glands. The latter are sebaceous in character and are arranged in rows along the inner margin of each lid. The tears themselves are alkaline in reaction and are chiefly composed of water (98.1 per cent.). They contain albumin (0.1 per cent.) mucin, epithelial cells (0.1 per cent.) and salts, principally sodium chlorid (0.4 to 0.8 per cent.).

CHAPTER LXIX

THE CORNEA, IRIS AND AQUEOUS HUMOR

The Refractive Power of the Cornea.—The cornea of the mammalian eye is a perfectly stationary structure possessing a certain curvature and refractive power. In the birds, on the other hand, it is set in a cartilaginous ring and its convexity may be altered by muscular activity. This fact indicates that in these animals it is made to serve as a powerful adjunct to the lens and thus, is in large part responsible for the keen sense of vision possessed by them. In the higher mammals, its importance is relatively slight, because its radius of curvature is only 7.8 mm.,² but this measurement pertains only to its central area situated directly in front of the pupil. Its marginal zone is of practically no optical importance even when the pupillar orifice is enlarged. It may be concluded, therefore, that the cornea, by virtue of its convexity, renders the entering rays of light slightly more convergent. In addition, it collects many of the otherwise too divergent rays, and directs them through the pupillar opening so that they may still be subjected to the refraction of the lens.

The Aqueous Humor.—It has been stated above that the anterior cavity of the eyeball consists of the anterior and posterior chambers, the former being situated in front of the iris and the latter, between the posterior surface of this partition and the anterior aspect of the

¹ Scimeni, *Archiv für Physiol.*, 1892, Suppl. 291.

² Helmholtz, *Physiolog. Optik*, Berlin, 1896.

lens and ciliary body. Many physiologists, however, believe that in adult life the iris lies in absolute contact with the lens and that the posterior chamber is merely a potential space. The transparent liquid filling this entire cavity, is known as the aqueous humor. Its quantity amounts to about 0.4 c.mm. and its specific gravity to 1.0053–1.008, which is the equivalent of a solution of sodium chlorid of a concentration of rather more than 1.0 per cent.¹ Its osmotic pressure is somewhat higher than that of the serum of the blood.² It may contain a few leukocytes, but only 0.08–0.12 per cent. of protein. This watery fluid also permeates the interstitial spaces of the gelatinous substance of the vitreous humor.

If a small manometer is connected with the anterior chamber of the eye by means of a tubular needle, it will be noted that the aqueous humor is held under a pressure of about 25 mm. Hg. This pressure is designated as the *intraocular pressure*. Its very obvious function is to render the eyeball tense so that its different refractive elements are fully unfolded. It need scarcely be emphasized that any unevenness in the cornea or an unduly relaxed ciliary body and ligament must greatly impair the usefulness of these structures for refraction. In addition, it may justly be assumed that the aqueous humor forms the nutritive medium for the lens, ciliary ligaments, and vitreous humor, because these structures are not directly supplied with blood. In certain pathological conditions, such as glaucoma, the intraocular pressure is enormously increased so that the eyeball can scarcely be indented with the finger. Clinically the tenseness of the eyeball is measured by means of the ophthalmotonometer. This instrument is pressed against the outer surface of the eyeball until its plate-like extremity causes a certain flattening at the point of contact. The pressure necessary to accomplish this end, is indicated by a tension spring.

A number of observations have been made which prove conclusively that the aqueous humor is continually renewed. Thus, any operation requiring an incision through the cornea, most generally leads to a loss of a considerable portion of this fluid which is again reformed in the course of a few days. Furthermore, it is possible to drain it off in a relatively steady stream by inserting a delicate cannula through the margin of the cornea. Its character is then gradually changed until it contains as much as 3 or 4 per cent. of proteins and becomes coagulable. It is commonly held that the aqueous humor is secreted by the epithelium of the ciliary body and its glands. From here it flows into the anterior recess of the posterior (vitreous) cavity of the eyeball, whence it finds its way through the clefts in the ligamentum pectinatum iridis into the angle of the anterior chamber. A portion of this fluid also escapes through the meshes of the ciliary ligament into the posterior chamber situated between the iris and the lens, and thence round the edge of the iris into the anterior chamber. The canal of Schlemm is the natural drainage tube of this space. A portion of this fluid also escapes into the lymph spaces of the iris and from here into the perichoroideal lymphatics. Still another portion is diverted from the ciliary glands into the interstitial spaces of the vitreous humor,

¹ Golowin, *Archiv für Ophthalm.*, li, 1900.

² Hamburger, *Osmotischer Druck und Jonenlehre*, 1904.

whence it finds its way into the lymphatics accompanying the optic nerve.

At all events, the outflow balances the production, so that the aqueous and vitreous humors are constantly held under a pressure of about 25 mm. Hg. This implies that these different drainage tubes are adjusted so as to place a considerable resistance in the path of the escaping fluid. In spite of this fact, however, it has been estimated that at least 6 c.mm. of new secretion are required per minute in order to maintain the pressure at the height just stated; moreover, it has been found that its quantity may be varied considerably by either raising or lowering the blood pressure. It cannot be doubted that this factor plays an important part in all processes of secretion, because it gives rise to the secretory pressure, but it seems that it is of special value for the formation of the aqueous humor. This fact suggests that this fluid finds its origin in large part in transudation.

The Iris.—The circumferential border of the iris is anchored to the eyeball immediately in front of the ciliary body. At this point it is continuous with the choroid coat as well as with the cornea through the ligamentum pectinatum. In its course through the aqueous chamber, its posterior surface is brought into close relation with the ciliary body and lens, while its anterior surface is everywhere fully exposed to the humor filling this cavity. Its inner margin surrounds an orifice, the pupil, through which the rays of light are enabled to enter the vitreous chamber. This orifice is nearly circular in shape and is placed somewhat nearer the nasal side of the eyeball. Under ordinary conditions its diameter measures about 4 mm., but is subject to constant changes in consequence of variations in the intensity of the light and the range of accommodation. A fuller discussion of this phenomenon will be given in a subsequent paragraph.

When looked at from in front, the iris measures about 11 mm. across, its inner margin being held at a distance of about 5 mm. from its circumference. Its thickness amounts to about 0.4 mm. Its body is formed by a stroma, consisting of a delicate framework of connective tissue, the fibers of which are in large part arranged in a radial direction. Anteriorly, the latter is lined with cells similar in structure to those covering the posterior limiting membrane (Descemet) of the cornea. Posteriorly, it is enveloped by two layers of epithelial cells, containing black pigment to which the blue color of the iris is due—blue because transmitted through the stroma. Its different shades of black, brown and gray, however, are caused by pigment cells which are scattered through the substance of the stroma.¹

The plain muscle fibers of the iris are arranged either circularly around the lumen of the pupil or radially to it. The former are most numerous right next to its margin, where they form a conspicuous sphincter, about 0.5 mm. in width. The latter form a layer of elon-

¹ Retzius, *Biolog. Untersuchungen*, 1893.

gated, spindle-shaped cells close to the pigment layer.¹ The blood-supply of the iris is derived from the long and anterior ciliary arteries, and its nerve supply from the long and short ciliary nerves. The origin and function of these nerves will be more fully described in a later paragraph.

The Function of the Iris.—The action of the iris may be compared to that of the adjustable diaphragm of an ordinary photographic camera. As such it possesses two functions, namely, to:

(a) Vary to size of the bundle of light entering the vitreous cavity, (1) during far and near vision or accommodation, and (2) during the alterations in the intensity of the light.

(b) Direct the rays of light through the center of the lens which is its most perfectly refracting part. Thus, by excluding the margins of lens, it prevents the occurrence of spherical and chromatic aberration.

It should be evident from the preceding discussion pertaining to the structure of the iris, that the contraction of its circular muscle fibers decreases the size of the pupil, while the contraction of its radial fibers increases it. Thus, we find at times that the margin of the iris is drawn almost completely over the lens, lessening the diameter of the pupil to less than 1 mm., and, at other times, that it is pulled outward until this aperture measures as much as 8 mm. across. The former change constitutes pupillar constriction, and the latter, pupillar dilatation. Obviously, these changes either diminish or increase the number of the light rays entering the vitreous chamber. A diminution in their number is made necessary (a) when the intensity of the light is great, and (b) when the eye is adjusted for a near object. Conversely, an increase in their number is required (a) in low intensities of light, and (b) when the object accommodated for is situated far away from the eye. Furthermore, inasmuch as these changes are effected as a result of reflex stimulation, we commonly speak of them as the light and accommodation reflexes.

The Light Reflex.—If a person is made to look alternately from a partially darkened surface into a light of moderate intensity, it will be observed that the pupil becomes small whenever the eye is more fully illuminated. An intense light, in fact, decreases its size to almost that of the point of a pin. It is true, however, that this change in the illumination must be effected rather rapidly, otherwise a decided alteration in the size of the pupil will not be produced.² Moreover, if the constriction has been continued for a longer time than 3 or 4 minutes, its size gradually increases, owing to an adaptation and fatigue of the constrictor mechanism. Obviously, the purpose of an enlarged pupil is to augment the receptive power of the retina by permitting as many rays as possible to strike it, while a constricted pupil serves to protect the retinal elements against an undue and injurious degree of stimulation.

¹ Grumert, *Arch. für Augenheilkunde*, xxxvi, 1898.

² Garten, *Pflüger's Archiv*, lxviii, 1897, 68.

In the case of the light reflex, the stimuli are received upon the retina, whence they are conveyed over the peripheral optic tract to the secondary or reflex optic center, situated in the anterior corpora quadrigemina next to the aqueduct of Sylvius.¹ To effect pupillar constriction they are transferred from here to the oculomotor nerve and the ciliary ganglion and nerves. Pupillar dilatation, on the other hand, is accomplished with the aid of the autonomic fibers and hence, these impulses must be diverted from the secondary optic center into the sympathetic system proper. Some authors also hold that the retina gives rise to two kinds of fibers, one group of which has to do with visual sensations proper and the other solely with the differences in the intensity of the light.² The time which is required for this reflex response of the iris, has been estimated at 0.04 to 0.05 second.

In man, as well as in those animals in which the optic fibers decussate in part, the light reflex is bilateral, so that light falling into one eye also gives rise to a diminution in the size of the pupil of the opposite organ. This is not the case in such animals as the horse, owl and rabbit, in which the crossing is complete.³ Furthermore, it has been noted that the substance of the iris, and especially in the lower forms, is extremely sensitive to light. Even small pieces of the iris of the frog or eel may be made to contract by simply permitting a beam of light to fall upon them.⁴ Clinically, the power of reaction of the pupils is usually tested by shading one eye in such a manner that its pupillar orifice can be observed beneath the cover. If the shaded eye is then uncovered, its pupil will be seen to constrict. The other eye also responds but not so intensely. This implies that the direct reaction to light is usually more profound than the consensual, as practised in this test.

From this discussion it may be gathered that the light reflex is abolished whenever the aforesaid reflex arc is broken at any point of its course. This calls to our minds the important fact that it is absent in *tabes dorsalis* (locomotor ataxia) and general paresis, while the accommodation reflex is preserved. This phenomenon is known as the Argyll-Robertson sign. Its explanation is not difficult if it is remembered that the nervous paths required for these two reflexes are totally different. Thus, the afferent arc in the case of the light reflex is formed by the optic nerve, whereas that concerned with the accommodation reflex is formed by the afferent fibers from the muscles of the eye. Inasmuch as the disease of *tabes dorsalis* is characterized by a progressive degeneration of the different spinal roots and tracts, it cannot surprise us to find that similar changes are finally induced in the optic path, thereby gradually blocking the impulses from the retina. At

¹ Hass, *Archiv für Augenheilkunde*, lx, 1908, 327.

² Behr, *Archiv für Ophthalmologie*, lxxxvi, 1913, 468.

³ Steinach, *Pflüger's Archiv*, xlvii, 1890, 313.

⁴ Arnold, *Physiologie*, ii, 1847; also see: Steinach, *Pflüger's Archiv*, lii, 1892, 495.

this time, the afferent paths having to do with the accommodation reflex, are still free from these degenerative alterations.

The Accommodation Reflex.—If a person is asked to accommodate alternately for near and far objects, it will be noted that the size of his pupil is decreased on near vision and increased on far vision. In the former instance, the number of rays entering the eye is diminished, but not at all sufficiently to impair our power of being able to make out the finer details of the object. This reduction in the size of the beam of light is, of course, entirely in keeping with perfect refraction, because the amount of light projected into the eye from any given object, increases inversely as the square of its distance. This implies that the phenomenon, constituting the accommodation reflex, is an associated action and is closely interlinked with the muscular efforts necessary for accommodation. These efforts consist in a convergence of the eyeballs effected by the contraction of the two internal recti muscles, and a contraction of the ciliary muscles, rendering the lens more convex. The afferent impulses which give rise to these reactions, are, of course, chiefly intracerebral in their origin, and do not involve the optic tract. Consequently, it appears that the constriction of the pupil on near vision is due to the fact that those motor discharges from the midbrain which evoke the contraction of the internal recti and ciliary muscles, overflow and simultaneously activate the neighboring center for the sphincter fibers of the iris.

In sleep the pupils are constricted in spite of the fact that the eyes are not stimulated by light. This fact may seem to be opposed to the view just expressed, unless it is remembered that the axes of the eyeballs are at this time turned inward and upward. Obviously, therefore, the initial constriction of the pupil during sleep is an associated movement, akin to that arising on near vision; in other words, the motor impulses which are required to deviate the eyeballs in the afore-said direction, also implicate the sphincter muscle of the iris.

The constriction of the pupil during the initial stage of anesthesia by ether or chloroform may be explained in a very similar way, because these agents give rise at first to a general excitation of the central nervous system. As soon as this primary effect has weakened, the pupil retains an intermediate size, but dilates immediately if the narcosis is deepened or is carried beyond its physiological limit. This danger point of narcosis may also be determined in other ways, for example, by noting the intensity of the reflexes and especially of those which are usually preserved during sleep and moderate narcosis. The one most commonly employed for this purpose is the corneal, consisting in a closure of the eyelids upon mechanical stimulation of the cornea. Among the agents which constrict the pupil, may be mentioned opium, and its alkaloid morphin, as well as the alkaloids eserin or physostigmin and pilocarpin. Among the dilators of the pupil should be cited the alkaloids of belladonna, namely, atropin and homatropin. A dilatation of the pupil commonly results in consequence

of depressions of the nervous centers, as well as in all conditions of nervous exhaustion, deep narcosis and comas. In dyspnea the pupils are large, but become smaller if this condition is changed into asphyxia. They are also enlarged by sensory impulses from the digestive and sexual organs, as well as by somatic and visceral sensations of pain. Even the cerebral cortex may influence their size without any apparent peripheral stimulation. Thus, it has been shown by Haab that if a person is made to look at a dark wall, while his eyes are illuminated by a constant light placed laterally in front of him, a marked constriction of his pupils results whenever his attention is called to the light. Quite similarly, his pupils may be made to dilate at any time by drawing his attention to the dark wall. Some persons, indeed, are able to constrict and to dilate their pupils by merely calling up a mental picture of bright and dark objects.

Spherical Aberration.—In discussing the focal points formed by spherical lenses, we have assumed that the rays emitted by a luminous object are sharply intersected behind the lens. Strictly speaking, this is not true, because the refraction of a lens differs somewhat in its different zones for the reason that its prismatic constituents are not centered with sufficient accuracy to act in perfect unison. The most perfectly refracting portion of a lens is its

FIG. 423.—DIAGRAM ILLUSTRATING SPHERICAL ABERRATION.

The iris being retracted the rays of light pass through the outer zone of the lens and are more sharply refracted than those traversing its center.

central area, having an aperture not exceeding 10° to 12° . If the size of this aperture is increased so that the rays can also traverse its peripheral segments, these rays will be brought to a focus in front of the focal point of those refracted through its center (Fig. 423). The intersections of these aberrated rays are called caustics. Obviously, their presence must render the image indistinct. This condition which is called spherical aberration, is also present in the lens of our eye, but is prevented from interfering with the formation of the retinal image by the fact that its peripheral extent is usually covered by the margin of the iris. In this regard, therefore, the latter performs the function of a stop, *i.e.*, it cuts off the rays from the circumference of the lens and allows only the passage of a concentrated central beam.

Chromatic Aberration.—If a bundle of light is projected through a lens, it will be noted that the rays traversing its central segment appear on its other side chiefly as white light, while those passing through its peripheral zone are dispersed into their different colored components. The image then appears surrounded by a colored margin. This effect

is to be expected, since light in passing from a rare into a dense medium suffers a retardation, and this diminution in its velocity affects its component rays differently, *i.e.*, those at the red end, with long wave-lengths, are refracted the least and those at the violet end, with short wave-lengths, the most. Inasmuch as a lens is composed of a series of prisms—and prisms split the white light in accordance with the unequal refrangibility of its simple color components—a spectrum must result (Fig. 424). Thus, white light, when passed through the edge of a biconvex lens, is dispersed so that its violet rays are brought to a focus (*V*) in front of its red rays (*R*), while the foci of its orange, yellow, green, blue and indigo are situated in between these two extremes. This condition which is called chromatic aberration, is also present in the lens of our eye, but cannot seriously interfere with the formation of the image, because the iris does not permit the rays of

FIG. 424.—DIAGRAM ILLUSTRATING CHROMATIC ABERRATION.

The iris being retracted, the rays of white light traversing the peripheral zones of the lens are split into their spectral components. The violet rays are focalized nearer the lens than the red.

light to pass through its more poorly refracting peripheral portion. By analogy, it may be concluded that the mydriatic eye receives chromatically aberrated images, because the edge of its lens is fully exposed to the entering beam of light. In artificial lenses this difficulty is often overcome by combining crown glass with flint glass. Inasmuch as the dispersive power of these glasses is very different, their individual dispersion may thereby be corrected without considerably lessening their total refractive power. This principle has been made use of by Dolland in the construction of the achromatic lenses, achromatism being the term applied to the phenomenon of the refraction of light without decomposition into its components.

It is a well-known fact that if we gaze at a red and violet light placed at the same distance in front of us, the former appears to be the more prominent and seems nearer to us. Clearly, this is merely an error of judgment, because since the red rays possess a greater

wave-length, a greater effort at accommodation is required in order to bring them to a precise focal point upon our retina.

Miosis and Mydriasis.—These terms are commonly employed to indicate that the size of the pupil has been varied by means of drugs or in consequence of pathological lesions. Miosis signifies pupillar constriction, and mydriasis, pupillar dilatation. The first condition is commonly associated with congestion and traumas of the iris, certain fevers, pulmonary congestion, and lesions of the sympathetic system. Among the miotics might be mentioned physostigmin (eserin), muscarin, and pilocarpin. Their action appears to be due to their power of stimulating the nerve fibers and corresponding receptor substance of the constrictor muscle. The mydriatics commonly made use of, are atropin, homatropin and cocain. The first two act by paralyzing the endings or receptor substance of the constrictor nerve fibers.¹ Cocain exerts a similar action, but only in larger doses, while in smaller doses, it stimulates the dilator mechanism. Mydriasis is also obtained in glaucoma, atrophy of the optic nerve and orbital diseases.

A mydriatic eye must, of course, be shielded against light, because it is temporarily unable to protect itself. In addition, it should be remembered that the mydriatics temporarily destroy the mechanism of accommodation, because they paralyze the ciliary muscle which is similarly innervated. Near vision, therefore, is practically impossible at this time. The miotics, on the other hand, also stimulate the ciliary muscle and keep the eye in a condition of forced accommodation. In the latter case, therefore, far vision is practically impossible.

The Innervation of the Iris.—The circular and radial fibers of the iris receive their nerve supply from the autonomic system, the relay stations nearest them being the ciliary ganglion and the superior cervical ganglion. Preganglionically, however, these fibers find their origin in the cerebrospinal system. As far as the sphincter iridis is concerned, it may be shown that its nerve fibers arise in the midbrain in the anterior part of the nucleus of the third cranial nerve. They make use of the third nerve as a highway to reach the ciliary ganglion, whence they continue onward postganglionically in the short ciliary nerves. The nerve fibers innervating the dilator mechanism of the iris, supposedly the radial muscle fibers, also arise in the midbrain, but their place of origin is not definitely known. From here they descend in the spinal cord, but leave this structure in the eighth cervical and the first and second thoracic spinal nerves to enter the sympathetic system by way of the rami albi communicantes. They then ascend to the superior cervical ganglion by way of the cervical sympathetic nerve and finally reach the Gasserian ganglion. Distally to this point they invade the ophthalmic branch of the fifth cranial nerve and its long ciliary branch.

¹ Langley, *Jour. of Physiol.*, xxxix, 1909, 235.

On excitation of the trunk of the third nerve, we obtain a constriction of the pupil, while the stimulation of the sympathetic nerve in its cervical portion, gives rise to pupillar dilatation. Obviously, therefore, the division of the former must evoke a dilatation of the pupil, and that of the latter, pupillar constriction. Under normal conditions, these two mechanisms are tonically set and oppose one another. Consequently, the removal of the constrictor impulses must allow the dilator impulses to gain the upper hand, while the division of the sympathetic nerve must permit the constrictor influences to exert their full-

FIG. 425.—DIAGRAMMATIC REPRESENTATION OF THE NERVES GOVERNING THE PUPIL.
(After Foster.)

II, optic nerve; cg, ciliary ganglion; rb, its short root from III, motor oculi nerve; sym., its sympathetic root; rl, its long root from V, ophthalmic branch of ophthalmic division of fifth nerve; sc, short ciliary nerves; lc, long ciliary nerves.

est power. It appears, therefore, that the constrictor and dilator muscles of the iris are arranged antagonistically to one another, in a manner similar to that of the flexor and extensor muscles of the extremities (Sherrington). Thus, inasmuch as it has been shown that the contraction of one set of skeletal muscles is usually facilitated by the inhibition of the other set, it may be assumed that a similar reciprocal relationship exists between the muscle fibers of the iris. Certain

evidence in support of this reciprocal action has been furnished by Anderson.¹

In this connection, it should also be mentioned that the oculomotor and short ciliary nerves innervate the ciliary muscle which is used in accommodation. For this reason, the excitation of this nerve really produces a double effect, *i.e.*, it constricts the pupil and also renders the lens more convex. Concurrently, its division must be followed not

FIG. 426.—SCHEMA SHOWING THE PATH OF THE PREGANGLIONIC AND POSTGANGLIONIC FIBERS TO THE CILIARY MUSCLE AND TO THE SPHINCTER AND DILATOR MUSCLES OF THE IRIS. (Modified from Schultz.)

only by pupillar dilatation but also by a flattening of the lens, which change renders it adapted for far vision.

CHAPTER LXX

THE CILIARY BODY AND LENS

The Ciliary Body.—The space between the ora serrata of the retina and the base of the iris is occupied by the ciliary processes of the choroid, its muscles, ligaments and glands. In this region, the choroid is considerably thickened, measuring 6 to 7 mm. across. In cross-section it displays a triangular outline, which is largely taken up by strands of plain muscle tissue, forming the ciliary muscle. These fibers are arranged in two ways, namely, longitudinally and transversely to the long axis of the eyeball. The former arise from the fore-part of the sclerotic coat close to the cornea, where they are attached to the ligamentum pectinatum. They pursue a course almost directly

¹ Jour. of Physiology, xxx, 1903, 15.

backward to be inserted in the choroid at and behind the ciliary process. The circular fibers are most numerous in the base of the ciliary body, and pursue a course circularly around the aperture in which the lens is suspended. They are most clearly in evidence in hypermetropic persons.¹

The aperture between the margins of the ciliary body is occupied by the lens. The latter is invested by a transparent and elastic capsule, measuring in front 6.5 to 25 μ in thickness. Its substance is composed of a firm central and softer cortical portion, both of which appear as hexagonal, prismatic lamellæ of homogeneous elastic tissue. A single layer of cuboidal cells, 2.5 to 10 μ in height, forms their outer investment. It is to be noted especially that the edge of the lens is not in absolute contact with the margin of the ciliary body, but remains at some distance from it, the intervening space being occupied by ligamentous bands which extend straight across from its capsule to the surface of the ciliary body. Furthermore, these ligamentous fibers pursue a peculiar diagonal course, some of them arising upon the posterior aspect of the ciliary body and terminating upon the anterior surface of the lens, while others arise upon the anterior surface of the ciliary body and end upon the posterior surface of the lens. We shall have occasion to refer to these data again later on, while discussing the accommodation of the eye for near objects.

The Process of Accommodation in Different Animals.—The purpose of the lens is to bring rays of light to a precise focus upon the retina. In this function it is aided in a slight measure by the other refractive media of the eye. But, since objects are situated at different distances from the eye, some means must be provided by which their images may be retained upon the retina; in other words, the eye must be able to accommodate itself to these varying distances. To approach this subject in the most logical way, inquiry should first be made regarding the manner in which the ordinary photographic camera may be adjusted for far and near objects. Two ways are open to us, namely, to move the sensitive plate either nearer to or farther away from the lens, or to move the latter either nearer to or farther away from the plate. A third method would be to permit the screen as well as the lens to remain stationary and to adjust the focal distance of the camera by interposing other lenses of different refractive power. This procedure, however, is not in common use, because it is less convenient than the other two.

In the animal kingdom, however, the third method is imitated by varying the convexity of the lens, while its position, as well as that of the retina, remains unchanged.

Indeed, the mechanism of accommodation is so diversified among the different animals that really all of the physical means just enumerated find their practical application.² To begin with, it should be noted that certain species lack

¹ Iwanoff, *Archiv für Ophthalmol.*, xv, 1869, 1.

² Beer, *Wiener klin. Wochenschr.*, 1898, No. 12.

this power altogether, while others possess it in only a very rudimentary degree. This is true of the frog, alligator, vipers and certain rodents. Inasmuch as these animals are chiefly dependent upon near vision and are nocturnal in their habits, their accommodation is never subjected to wide variations. Furthermore, their associations are so poorly developed that there is really no necessity for their being able to discern the exact details of an object, as long as they can perceive its simplest movements. They are essentially shadow-animals.

In the cephalopod molluscs, such as sepia, we observe that the thin globe of the eye is strengthened by a transverse ring of cartilage, immediately adjoining an exceptionally delicate ring of tissue (Fig. 427). The anterior wall to this eye contains bands of meridional muscle fibers which are attached to the cartilaginous ring (C) and are inserted in the ciliary body. On contraction this muscle pulls the entire anterior half of the eye backward, in this way bringing the lens nearer the retina. This movement necessitates, of course, a redistribution of the intraocular pressure which is made possible by a bulging of the thinned wall of the eyeball directly behind the cartilaginous ring. It need scarcely be mentioned that this approximation of the lens to the retina enables this animal to accommodate for far objects.

FIG. 427.—DIAGRAM ILLUSTRATING THE PROCESS OF ACCOMMODATION IN THE EYE OF SEPIA.

The anterior half of the eyeball is drawn toward the cartilaginous ring C on far vision.

FIG. 428.—DIAGRAM ILLUSTRATING PROCESS OF ACCOMMODATION IN THE EYE OF THE FISH.

C, cornea; L, the lens is pulled toward the retina on far vision by R, the musc. retractor lentis.

The eyes of the amphibians and many reptiles, such as the snakes, are normally adjusted for far vision. In these animals accommodation is effected by increasing the distance between the lens and the retina. This change is accomplished in this way: As the ciliary muscle contracts, it pulls the sclerotic-corneal junction backward, thereby increasing the pressure in the vitreous cavity. In consequence of this increase in pressure, the lens is pushed forward into the aqueous cavity and approaches the cornea. An equalization of the pressure in this chamber is made possible by a displacement of the aqueous humor into its lateral angle which has just been enlarged by the retraction of the ciliary body. It is evident that this removal of the lens from the retina must increase the posterior focal distance and must accommodate the eye for near objects.

The eyes of the fishes are normally set for near objects (Fig. 428). They are not in possession of ciliary processes nor of ciliary muscles, and their almost spherical lens is suspended in the visual axis by means of flat bands of connective tissue, forming the so-called suspensory ligament. The lower and inner pole of the lens gives attachment to a number of horizontal strands of muscle fibers which on contraction pull the lens backward, thereby diminishing the distance between it and the retina. This muscle, known as the retractor lentis, lessens the posterior focal distance of these eyes and accommodates them for far objects. Consequently,

the fish's eye may be made extremely myopic by surrounding it with air, while that of a terrestrial animal may be rendered hypermetropic by placing it in water.

The birds are noted for their exceptionally accurate and rapid accommodation. Their eyes are normally set for distant objects, and their accommodation for near objects is made possible not by changing the position of the lens, but by increasing its convexity and hence, its refractive power. The lens is enabled to change its shape by lessening the tension under which it is ordinarily held. This relaxation is effected by pulling the sclerotic-corneal junction backward. Inasmuch as the suspensory ligament of the lens is attached to this area of the eyeball, this retraction must relax it, thereby permitting the lens to become more convex on account of its inherent elastic power. A special muscle, known as Crampton's muscle, controls this retraction. It is also of interest to note that the fibers composing it, are of the striated variety and are, therefore, under a more direct and exact control of the higher centers than the ciliary muscle of the mammals. This structural peculiarity accounts for the rapidity of the accommodation in birds which enables them to swoop down from great heights to catch their prey. In addition, the birds of prey possess the power of increasing the convexity of their cornea. A special muscle is provided for this purpose.

The Accommodation of the Human Eye.—It has been shown by Helmholtz that the accommodation of the mammalian eye is effected by an alteration in the convexity of the lens, chiefly of its anterior part. Naturally, an increase in its convexity gives rise to an increase in its refractive power and hence, to an accommodation for near objects. Two theories have been formed in explanation of this phenomenon, namely:

(a) The greater curvature of the lens on near vision is due to the fact that it is subjected to a greater tension by the components of the zonula Zinnii.¹

(b) The greater convexity of the lens on near vision is caused by the fact that the tension under which it is ordinarily held is diminished at this time.

The second view is the one commonly accepted to-day. It is usually designated as the detention theory of Helmholtz.² It is believed that the contraction of the ciliary muscles causes the ciliary body and adjoining choroid to be pulled forward. In consequence of this displacement, the ciliary ligaments are loosened, permitting the lens to bulge forward. Besides, it must be evident from figure 429 that this forward movement of *B* must give rise to a relaxation especially of those ligamentous bands which extend between the posterior surface of the ciliary body (*CB*) and the anterior marginal zone of the capsule of the lens (*L*). As a result of this detention of its peripheral area, the mass of the entire lens adjusts itself and assumes a more spherical shape. Its anteroposterior diameter is increased thereby.

While it is a matter of common observation that even lenses with fluid contents tend to assume a spherical outline,³ it is to be noted that the lens of the mammalian eye is invested by an elastic capsule. It is this investment which is chiefly responsible for the aforesaid

¹ Schön, Pflüger's Archiv, lix, 1895, 427; also: Tscherning, *Optique physiologique*, Paris, 1897.

² *Physiol. Optik*, ii, 136.

³ Schweigger, *Archiv für Augenheilkunde*, xxx, 1895, 276.

changes in the lens. We have seen that the ciliary muscle is made up of meridional and circular fibers. Even a casual study of their course must show that the former are the principal factors concerned in this detention, but it cannot be denied that the circular fibers are a most important adjunct, because they fix the base of the ciliary body so that the longitudinal fibers can gain a firmer hold upon this structure and pull it forward. That a movement of this kind actually takes place has been proved by Henson and Völker.¹ Fine needles were inserted through different segments of the equatorial region of the eyeball which, on stimulation of the ciliary body, showed movements indicative of a forward displacement of the choroidea.

FIG. 429.—DIAGRAM ILLUSTRATING THE PROCESS OF ACCOMMODATION IN THE HUMAN EYE.

C, cornea; *L*, lens; *J*, iris; *CL*, ciliary ligament; *CB*, ciliary body; *Ch*, choroid; *R*, retina; *S*, sclera. On near vision the ciliary muscle contracts, drawing the region *B* nearer to region *A*. The tension upon the ciliary ligament being diminished thereby, the lens assumes a more spherical shape, chiefly in the direction of the cornea. This change is indicated in red.

Proofs of Accommodation.—When the eye is at rest, it is accommodated for far objects. We may convince ourselves of this fact by suddenly opening the eyelids after they have been held shut for a short time. We then become conscious of a relaxed vision, *i.e.*, of an accommodation for far objects, and also of a distinct effort to direct the eyes to a near object. During relaxed vision, the suspensory ligaments are placed under a certain tension, thereby retaining the lens in a somewhat flattened condition. This may be proved by measuring the anterior curvature of the lens before and after the excision of the eye. It is very obvious that a lens freed from its attachments, possesses a more spherical outline than one still in its normal position.

The increased curvature of the lens, and especially that of its an-

¹ Archiv für Ophthalm., xix, 1873, 156.

terior portion, leads to a movement of this surface toward the cornea. This change may be studied in any human eye, if the person under observation changes his accommodation repeatedly from far to near objects. The most obvious alteration consists in a forward displacement of the margin of the iris, caused by the forward bulging of the anterior surface of the lens. The cornea, on the other hand, undergoes no change whatever. These observations may then be repeated by actually measuring the curvature of these refracting surfaces on far and near vision.

Changes in accommodation may also be effected by stimulating the excised eye electrically. Most commonly we employ for this purpose the eye of a terrapin, which is adjusted under a magnifying glass by means of two fine needles inserted vertically through its corneal sclerotic junction. These needles are connected with the secondary coil of an inductorium (Fig. 430). On stimulation with single induction shocks, it will be seen that the iris is pushed far forward into the aqueous humor, while the anterior portion of the lens bulges prominently through the pupillar orifice.

FIG. 430.—DIAGRAM ILLUSTRATING THE CHANGES IN THE LENS ON STIMULATION OF THE CILIARY BODY.

A, the eye at rest; B, during stimulation the lens forces its convexity through the pupillar orifice, pushing the iris forward.

One of the most interesting proofs of accommodation has been furnished by Langenbeck.¹ It consists in determining the form, size and position of the images of a brilliant object reflected from the different refracting surfaces of the eye. Thus, if a candle is held at a distance of about 50 cm. laterally in front of the eye of the observed person, while the observer places himself at an angle of 15° to 20° to the visual axis opposite the candle, three images of this object will be obtained, namely,

- (a) A bright upright image from the surface of the cornea,
- (b) a large upright but faint image from the anterior surface of the lens, and
- (c) a small inverted and faint image from the posterior surface of the lens.

The first is very prominent, while the other two are less distinct, but can usually be seen without much trouble by properly adjusting the position of the candle. With this arrangement, the large, faint upright image from the anterior surface of the lens, occupies the center of the pupil, while the faint inverted image from the posterior surface of the lens lies very close to the margin of the pupil opposite the observer. The relative size and position of these images having been clearly ascertained, the observed person is asked to accommodate alternately for near and far objects (Fig. 431). When this is done, it

¹ Klin. Beiträge zur Chir. und Ophthalm., Göttingen, 1849; also see: Helmholtz, Monatsber., Berliner Akad., 1853.

will be found that on near vision the corneal image (*a*) retains its position, size and form, while the one reflected from the anterior surface of the lens (*b*), becomes smaller in size and more rounded, and moves toward the corneal image. A very slight diminution in size is also displayed by the image reflected from the posterior surface of the lens

FIG. 431.—REFLECTED IMAGES OF A CANDLE FLAME AS SEEN IN THE PUPIL OF AN EYE AT REST AND ACCOMMODATED FOR NEAR OBJECTS. (*Williams.*)

(*c*). It need scarcely be mentioned that these changes are associated with a constriction of the pupil (Descartes, 1637), and that all the aforesaid alterations are reversed on far vision. Since near vision is an active muscular process, it is accomplished less speedily than the accommodation for far objects.

FIG. 432.—DIAGRAM EXPLAINING THE CHANGE IN THE POSITION OF THE IMAGE REFLECTED FROM THE ANTERIOR SURFACE OF THE CRYSTALLINE LENS. (*Williams, after Donders.*)

The lesson to be derived from this experiment is that the curvature of the cornea remains absolutely the same, while that of the posterior surface of the lens suffers only the slightest possible alteration. By far the greatest change takes place at the anterior surface of the lens, which, on near vision, becomes more convex and therefore forces the

image closer to the cornea, rendering it at the same time more globular. These observations may be repeated under more favorable conditions by making use of a darkened triangular box, known as the phacoscope (Helmholtz). The eye to be observed is placed in the orifice at *A* (Fig. 433) and is directed alternately to a needle situated in orifice *B* and to a distant object placed in the prolongation of this visual line. Orifice *C* is beset with two prisms which throw a beam of light into the observed eye. The observer's eye studies these images through orifice *D*. They appear as indicated in Fig. 434.

Another most instructive phenomenon is the so-called wabbling of the lens,¹ which consists in a declination of the lens on forced near vision of from 0.28 to 0.3 mm. This phenomenon clearly proves that accommodation diminishes the tension under which the lens is held, allowing its weight to force it out of the central axis of the eyeball. The direction of this declination depends

FIG. 433.

FIG. 433.—DIAGRAM ILLUSTRATING COURSE OF THE RAYS THROUGH THE PHACOSCOPE. *A*, observed eye; *B*, opening allowing accommodation for near and far objects; *C*, source of light; *D*, observer's eye. 1, images from cornea; 2, anterior surface of lens; 3, posterior surface of lens.

FIG. 434.

FIG. 434.—DIAGRAM OF REFLECTED IMAGES AS SEEN IN PHACOSCOPE.

A, during far vision; *B*, on near vision; 1, image from cornea; 2, image from anterior surface of the lens; 3, image from posterior surface of the lens.

of course upon the position of the head. Thus, when in the erect position, near vision would allow the lens to drop downward commensurate with the degree of accommodation. Subjectively we observe this phenomenon only under unusual conditions, for example, when endeavoring to form a focus of those shadows which are ordinarily produced by opaque bodies floating through the aqueous or vitreous humor. These particles then appear to execute jerky motions in space.

In addition, it might be mentioned that the mechanism of accommodation may be altered by drugs. The mydriatics atropin, homatropin and cocain paralyze the ciliary muscle simultaneously with the

¹ Hess, *Archiv für Ophthalm.*, xliii, 1897, 477.

constrictors of the pupil and retain the eye in a condition adapted for far vision. Physostigmin, on the other hand, stimulates this muscle and renders the eye near-sighted.¹

Scheiner's Experiment.—An experiment which illustrates the process of accommodation, as well as the projection of visual impressions, is the one described by Pater Scheiner. Two small holes are made in a cardboard, the distance between them being less than the diameter of the pupil. The eye then looks at two pins placed one behind the other, at a distance of 18 cm. and 60 cm. respectively.

FIG. 435.—DIAGRAM TO ILLUSTRATE SCHEINER'S EXPERIMENT.

The continuous lines indicate the course of the rays from the object for which the eye is accommodated.

If one pin is focalized sharply, the other appears double. A glance at Fig. 435 will show why this must be so. Thus if the eye is directed upon the near pin *A*, the far pin *B* is brought to a focus in the vitreous humor after which the rays again diverge and strike the retina in two places, *C* and *D*. If opening 1 is now blocked, the lower retinal image *D* disappears and hence, also the image projected into space on the side of the block. If the eye is now accommodated for the far pin *B*, the near pin *A* is focalized behind the retina, the still divergent rays striking the retina in points *E* and *F*. It will be seen that blocking opening 1 will now cut out the upper retinal image *E*, and hence, the image projected into the visual field opposite to the block.

The Changes in the Shape and Refractive Power of the Lens.—The changes in the shape of the lens may be deduced from the following

¹ One of the earliest theories pertaining to accommodation proposes that this process necessitates a lengthening and shortening of the entire eyeball, brought about by the pressure of the contracting extrinsic muscles of the eye. By a process of exclusion, we have shown above that the lens is the essential factor concerned in accommodation. It would be difficult to disprove the facts brought forth in support of this view; moreover, since an accommodation for an object held at a distance of 15 m., would entail a lengthening of the eyeball of not less than 2 mm., it seems hardly possible that such a change could be brought about by means of the normally contracting muscles of the eyeball. Electrical stimulation, performed under experimental conditions, might, however, accomplish this end. This view has recently been resurrected by Bates (New York Med. Jour., ci, 1915).

ophthalmometric measurements, giving the radius of curvature of the chief refracting media:

	Near vision	Far vision
Radius of curv. of cornea.....	8 mm.	8 mm.
Radius of curv. of ant. surface of lens.....	10 mm.	6 mm.
Radius of curv. of post. surface of lens.....	6 mm.	5.5 mm.

The lens of a relaxed eye measures 3.025 to 4.43 mm. in thickness, average 3.6 mm. On near vision, its anterior surface is carried forward through a distance of 0.36 to 0.44 mm.; hence, it will be seen that the thickness of the lens, when accommodated for near objects, is increased by about 0.4 mm., *i.e.*, on the average from 3.6 mm. to 4.0 mm. This implies that its anterior surface is then situated at a distance of only 3.2 mm. behind the cornea, while this same distance in the eye at rest measures 3.6 mm. Its posterior surface lies 7.2 mm. behind the cornea during far vision and retains this position, at least practically so, during near vision.

This change in the shape of the lens is dependent upon its inherent elasticity, and especially upon that of its capsular investment. This property it is permitted to bring into play as soon as the tension under which it is ordinarily held by the structures of the zonula Zinnii, is diminished. Since its refractive power is increased thereby, the entering rays of light must be rendered more convergent. Under ordinary conditions we express the refractive power of a lens in terms of its principal focal distance. A lens possessing a focal distance of one meter, is said to have a refractive power of one diopter (D.). Taking this value as a unit, a lens with a focal distance of 50 cm. possesses a refractive power of 2D., one with a focal distance of 10 cm., a refractive power of 10D., and conversely, one with a focal distance of 10 m., a refractive power of 0.1D. ($\frac{1}{10}$ D.).

Range of Accommodation.—The ciliary mechanism fulfills the purpose of bringing any object in space to a precise focus upon the retina, but, naturally, it cannot simultaneously produce a sharp image of two objects which are situated at different distances from it. We can readily convince ourselves of this fact by looking at a distant object through a network of fine wire held near our eyes. If we glance at the distant object, the wire network loses its clear contours. Contrariwise, if we look at the network, the object becomes blurred.

The distant point in space at which an object is still clearly discernible, is called the *far-point* or *punctum remotum*. Quite similarly, the point nearest the eye at which an object still produces a perfectly clear impression, is known as the *near-point* or *punctum proximum*. In between these two extremes lies the range of distinct vision, or *range of accommodation*. Any object situated beyond the far point or inside the near point, cannot be brought to a precise focal point upon the retina and must, therefore, appear blurred.

The Limit of Accommodation of the Normal Eye.—Inasmuch as the normal or emmetropic eye, when at rest, is adjusted so as to focus

parallel rays coming from the distance, its far point must lie at the horizon. Consequently, its location must vary with those outside factors upon which the visibility of objects ordinarily depends. Practically, however, it has been found that an eye can also perceive objects without accommodation which are situated at a distance of only 6 to 10 m. from it. The deduction to be drawn from this fact is that even objects situated at this short distance, emit a large number of parallel rays which the eye is able to intersect upon the retina without actually increasing its refractive power. In this action, however, the different refractive media are aided by the material depth of the receptor. In other words, the rods and cones of the retina upon which the light impinges, do not form a true plane but possess a certain depth, allowing us to vary the anterior focal distance in a slight measure without actually causing the posterior focal point to fall entirely outside this layer.

If the object is now moved nearer to the eye than the aforesaid distance, the mechanism of accommodation is immediately brought into play with the result that the now divergent rays are still brought to a focus upon the retina.¹ The closer the object is made to approach the cornea, the greater will be this effort at accommodation until its physiological limit has been reached. As has just been stated, the nearest point at which the eye is still capable of forming a distinct image, is called the near point. Beyond this inner limit the rays of light emitted by an object, are so divergent that they can no longer be brought to a sharp intersecting point upon the retina. The image then appears merely as a diffused area of light which fails to give a proper visual impression.

The determinations of the near-point by means of the ophthalmometer have shown that it does not retain a constant position, but varies not only with age, but also with the general condition of the body and local defects in refraction. At birth, the lens is rather spherical in shape; hence, the infant's eye should really be adjusted for near objects, were it not for the fact that the eyeball is at this time still too small. In reality, these two factors are adjusted in such a way that this eye is somewhat far visioned. Beginning at about the age of 10 years, the near point recedes gradually with advancing years and more markedly between the fortieth and fiftieth year. This observation is more fully illustrated by the following figures:

Age

10 years—	7 cm. in front of cornea, equalling	14	D. refr. power
20 years—	10 cm. in front of cornea, equalling	10	D. refr. power
30 years—	14 cm. in front of cornea, equalling	7	D. refr. power
40 years—	22 cm. in front of cornea, equalling	4.5	D. refr. power
50 years—	40 cm. in front of cornea, equalling	2.5	D. refr. power
60 years—	100 cm. in front of cornea, equalling	1.0	D. refr. power

¹ The term retina is employed here as well as elsewhere, although it is to be clearly understood that we are actually referring to the sensitive inner layer of the retina, namely to the rods and cones.

This gradual restriction of the range of accommodation is generally explained by saying that the lens loses its elasticity with advancing years. While this is true, the same may be said regarding the structures of the zonula Zinnii and the constituents of the ciliary body. Senescence is a common phenomenon in nature and begins with infancy, although dimmed at this time by the phenomenon of growth. Actual disturbances in vision, however, do not arise until the near point has receded beyond 25 to 30 cm., *i.e.*, until about the forty-fifth year. At this time, most persons experience certain difficulties in accurately focusing small print. This condition is designated as *old-sightedness* or *presbyopia*. It indicates that our ciliary mechanism is no longer capable of rendering the lens sufficiently convex to permit us to bring near objects to a precise focus upon the retina. Our accommodation for far objects remains of course unimpaired. This difficulty in refraction may be remedied by the employment of a biconvex lens of a strength just sufficient to overcome the senile flatness of the lens.

Late in life the lens frequently undergoes certain retrogressive changes which lead to an opacity of its substance. When fully developed, this condition, known as cataract, destroys the vision completely, because it prevents the rays of light from entering the fundus of the eye. The removal of this now useless lens, immediately adjusts the eye for far vision, because it is then wholly dependent for its refraction upon the cornea and the aqueous and vitreous humors. All three media together, however, do not equal the refractive power of a normal lens. An eye of this kind may again be converted into a more useful organ by placing a biconvex lens of 10 or 11 diopters in front of it. The same correction must be made for an eye, which has never been in possession of a lens. This inherited condition is known as *aphakia*.

This discussion introduces the question of whether the near point or far point, as determined for uniocular vision, remains the same when both eyes are used, as in normal binocular vision. Hess has proved this to be the case whenever the two visual axes are converged in a symmetrical manner, but not when we look laterally outward. The near point of binocular vision is then situated at a somewhat greater distance from the eyes.

The Innervation of the Ciliary Muscle.—Like the sphincter pupillæ, the ciliary muscle derives its motor impulses from the anterior part of the nucleus of the oculomotor nerve in the midbrain. These preganglionic fibers are relegated to the ciliary ganglion, where they end in arborizations around other cells. Postganglionically, these fibers are continued as elements of the autonomic system and reach their destination by way of the short ciliary nerves. This distribution accounts for the close interaction between the ciliary muscle and the constrictor of the pupil; near vision, as has been shown above, being associated with a constriction of the pupil. It also explains the simultaneous con-

vergence of the visual axes of the two eyes on near vision by the recti interni muscles. All these actions are controlled by a common co-ordinating center.

It is also of interest to note that the activity of this center is under the guidance of the will and is, therefore, controlled by the cerebrum. This must seem peculiar, because the effector, the ciliary muscle, is composed of smooth muscle tissue. It must be admitted, however, that these reactions are usually preceded by visual sensations. In other words, most persons cannot effect these changes in the eyes unless guided by objects in space. This observation might lead us to suppose that the act of accommodation is a simple reflex, just because the motor actions upon which it is based, seem to necessitate certain sensory impressions. In reality this is not true, because we can easily learn to accommodate without first directing our eyes to near and far objects by simply making volitional efforts in a dark room, or after our eyes have been shaded. Under ordinary conditions, therefore, the process of accommodation belongs to the group of the psychical reflexes or association reflexes. As such, it occupies a position intermediate between the voluntary responses effected by means of striated muscle, and the perfectly involuntary reactions accomplished with the help of smooth muscle.

CHAPTER LXXI

THE RETINA

The General Structure of the Retina.—The retina is a delicate membrane containing those elements which are absolutely essential for the reception of the rays of light and for the transfer of the impressions evoked by them to the center of sight in the occipital cortex of the cerebrum. It occupies the space between the choroid coat and the hyaloid membrane of the vitreous humor, and extends forward to near the posterior margin of the ciliary body. It terminates here in the so-called ora serrata. Its thickness increases gradually from before backward, namely from 0.1 mm. near the ciliary body to 0.4 mm. upon the posterior expanse of the eyeball.

In cross-section it presents eight distinct layers, namely:

- (a) The fiber layer, composed of nerve fibers striving toward their common point of exit, the porus opticus.
- (b) The layer of nerve cells, forming the ganglion nervi optici.
- (c) The inner molecular layer (stratum reticulare int.).
- (d) The inner nuclear layer, formed by bipolar cells (stratum granularum int.).
- (e) The outer molecular layer (stratum reticulare ext.).
- (f) The outer nuclear layer (stratum granularum ext.).
- (g) The layer of rods and cones.
- (h) The layer of hexagonal pigment-cells (stratum nigrum).

The nerve fibers derived from the different regions of the hemispherically expanded retina, leave at the optic pore where they pierce the other two coats of the eyeball and are continued onward as the optic nerve. Inside this point they are not in possession of a medullary sheath nor of a neurolemma. Most of these fibers are formed by the axis cylinder processes of the cells of the second layer, but some also originate in the inner molecular and inner granular layers. The ganglion cells of the second layer differ greatly in their size and shape, their single unbranched axones entering the fiber layer. They are especially numerous in the vicinity of the yellow spot, where they are arranged in three consecutive rows. The inner molecular layer is granular in its appearance and is made up of the arborescent

FIG. 436.—DIAGRAMMATIC SECTION OF THE HUMAN RETINA. (Schultze.)

terminations of the processes of the cells constituting the two neighboring layers. The inner nuclear contains two types of closely packed cells of which the bipolar type is the most conspicuous. Their inner processes usually extend to the internal molecular layer within which they terminate in the vicinity of its ganglion cells. Their outer processes are usually thicker and pursue a more direct course to the outer molecular layer, where they arborize together with the horizontal cells of the inner nuclear layer. The outer molecular presents an appearance similar to that of the inner molecular, but is not quite so thick. The outer nuclear layer consists of nuclear corpuscles having an oval or elliptical shape. They are known respectively as the rod-granules and cone-granules. The former are the more numerous and appear as swellings upon the delicate fiber emitted by the rods of the outermost

layer of the retina. The cone-granules are more pyriform in shape, non-striated and lie in close opposition to the external limiting membrane and the bases of the cones. Their inner processes are continued into the outer zone of the outer molecular layer, where they terminate in a prominent varicosity.

The outermost layer of the retina consists of the rods and cones. The former are elongated cylindrical in shape and measure about 0.06 mm. in length and 0.002 mm. in width. The latter are shorter and thicker and measure 0.035 mm. in length and 0.006 mm. in breadth. Both present an outer and an inner limb, the former being imbedded in the neighboring pigment layer. The processes derived from the inner limbs of the rods, pass into the nuclei of the outer nuclear layer. A central fiber extends from here into the outer molecular layer, where it ends in a knob-like structure. The processes from the inner limbs of the cones traverse the external nuclear layer and terminate in a broad expanse in the outer molecular layer. At this point connection is made with the bipolar cells of the inner nuclear layer by means of short fibers.¹ But, since the retina contains many millions of rods and cones, while the optic nerve embraces only about 48,000 nerve fibers, these peripheral axons must gradually become confluent.²

The cells of the pigment layer measure 12 to 18 μ in diameter, but decrease in size near the yellow spot. Their outer surfaces are smooth, and while their outer portions are practically free from pigment, their inner marginal zones are packed with it and present filamentous prolongations extending inward along the limbs of the rods and cones. The former are almost completely surrounded by this pigmented material.

While we shall have occasion to refer to these structural details later on in connection with the theories pertaining to vision, attention is called to the fact that the retina is something more than a simple sense organ; in fact, its complex structure would lead us to believe that it is as truly a subdivision of the brain as is the cerebral hemisphere itself. For the same reason, it may be concluded that the optic nerve is not a simple nerve but a true tract of the cerebrum. In this system the rods and cones form the receptors, and hence, constitute its neurones of the first order, while the cells composing the internal granular layer, are its neurones of the second order and those of the zone of ganglion cell, its neurones of the third order. The latter convey the impulses to the ventral aspect of the brain by way of the optic nerve, whence they are relayed to: (a) the cortical center for vision through the thalamic radiation, (b) the roof of the colliculus

FIG. 437.—I, A Rod; II, A Cone of MAMMALIAN RETINA; h, EXTERNAL LIMITING MEMBRANE. (G. Greeff.)

¹Ladd and Woodworth., Elements of physiol. Psychology, New York, 1911.

²Salzer, Sitzungsber., Wiener Akad., lxxxi, 1880, 3.

of the midbrain for purposes of reflex action, and (c) the pulvinar and lateral geniculate bodies of the region of the thalamus. These connections convert the optic nerve into a correlation path which is comparable to the lemniscus system.

The Blind Spot.¹—The retina derives its nerve supply from the optic nerve which pierces the eyeball in the optic disc or porus opticus. Beginning at this point, its fibers spread out fan-like across the entire

FIG. 438.—SECTION THROUGH THE PLACE OF ENTRANCE OF THE OPTIC NERVE (B), TOGETHER WITH THE OPHTHALMOSCOPIC VIEW OF THE DISC (A), TO SHOW THE CORRESPONDING PARTS OF THE TWO. (Fuchs, after Jaeger.)

cd, Lines of correspondence; *b*, depression in center of disc; *r*, retina; *ch*, choroid; *si, so*, inner and outer parts of the sclerotic coat; *s, ci*, a ciliary artery cut longitudinally; *a, v*, central artery and vein; *sd*, subdural space; *sa*, subarachnoid space; *du*, dural sheath; *ar*, arachnoidal sheath of nerve; *p*, pial sheath; *n*, nerve-bundles; *se*, septa between them.

expanse of this membrane. The circumference of this disc is slightly elevated, while its center shows a depression from which the blood-vessels pass radially outward toward the ora serrata. Its diameter measures about 1.8 mm. When looked at from in front, it appears as a whitish circle surrounded by a dark ring, the latter indicating the line where the pigmented choroid begins. Inasmuch as this entire area is composed solely of nerve fibers, blood-vessels and reticular tissue

¹ The blind spot of the eye was discovered by Mariotte in 1668 (Mém., Acad. de Paris, 1669).

and contains no other retinal element, it is insensitive to light. Nerve fibers as such cannot be activated by the ethereal impacts of light.

The presence of the blind spot may be demonstrated in several ways. Donders,¹ for example, projected the rays of a small flame alternately upon the entrance of the optic nerve and upon the general expanse of the retina. The individual received no sensation of light, when the image was localized upon the former area. Another way is this: If the left eye is closed, while the right eye gazes steadily at the crossed lines of Fig. 439, the white circle situated about 8 cm. to the right of this mark, becomes invisible as soon as the figure is held at a distance of about 25 cm. from the eye. In other words, the disappearance of this circle can only take place if the figure is placed at a distance about 3 times greater than that between the cross and the circle. If the latter are separated more widely, the figure must be moved farther away from the eye and vice versa. Furthermore, if the opposite eye is employed, the figure must be reversed, because the optic nerve leaves the eyeball on the nasal side of a horizontal line drawn through the anterior and posterior poles of the eye.

FIG. 439.—DIAGRAM TO DEMONSTRATE PRESENCE OF BLIND SPOT IN THE VISUAL FIELD.

Fix the cross with the right eye; bring figure closer to eye until the white dot disappears. (*Helmholtz*.)

Obviously, therefore, the visual field of each eye must possess an indifferent area corresponding to the projection of the optic disc into space. But, this projection does not give rise to a dark patch in space, nor to a similar impression in consciousness but appears merely as an area devoid of stimulation, *i.e.*, as a small hole in the visual field without any apparent details. Under ordinary conditions, this defect is not apparent, because, when gazing at an object, we always deviate the eye in such a way that the rays of light emitted by it fall upon the most sensitive part of the retina, which is the yellow spot. Consequently, the blind spot must occupy at this time a place in our indirect field of vision. In binocular vision, the conditions are even more favorable, because while an object or part of it, may fall upon the blind spot of one eye, it cannot also do this in the opposite eye. Hence, the blank in the field of vision of one eye is always filled in by the other eye. A similar compensation is effected in the psychic center for vision.

The size and shape of the blind spot may be mapped out as follows: Close the left eye and fix the right eye upon a mark upon a sheet of

¹ Onderzock., *Physiol. Labor.*, Utrecht, vi, 1852, 134.

white paper held at a moderate distance vertically in front of it. By now slowly moving the head of a pin inward along the horizontal plane of this field, a point will presently be reached when it suddenly disappears from the view and later on, a second point, when it reappears. By repeating this procedure along the vertical and oblique planes, the margins of this indifferent area in space may be mapped out in its entirety (Fig. 440). By projection it then becomes possible to calculate the position and size of the optic disc. It will be found that objects of the size of a 5 cent piece may be made to disappear when held at a distance of about 25 cm., and objects of the size of the head of a man, when placed at a distance of about 2 m. The slight irregularities in the contours of this projected figure of the blind spot are due to the interception of the light rays by the blood-vessels as they cross the margin of the optic papilla.

FIG. 440.—FORM OF THE BLIND SPOT. (Helmholtz.)

The Yellow Spot.—About 3.5 mm. or 15 degrees outside the blind spot and 1 mm. above the level of a horizontal line drawn through the posterior pole of the eyeball, lies the most sensitive area of the retina. It is known as the macula lutea, while its somewhat depressed center is designated as the fovea centralis. The latter measures about 0.2–0.4 mm. in diameter, and the entire area about 2 mm. Histologically it is noted that the retina of this region is greatly thinned, retaining in the fovea centralis merely the layer of the rods and cones. Moreover, it is observed that this particular area is made up exclusively of cones which are much larger than those situated in the outlying districts of the retina. They are so closely packed that they give the appearance of a mosaic of hexagonal prisms (Heine). The fibers leaving these elements, pursue an oblique course and push the inner layers of the retina farther toward the circumference of the macula lutea, so that the cones are more fully exposed to the entering rays of light.¹ Outside the macula the cones decrease and the rods increase in number. When these histological characteristics are compared with those of the blind spot and those of the outlying districts of the retina, it must be concluded that the cones are the most important factor in vision. This inference finds further support in

¹ Rochon-Duvigneaud, Archives d'anat. micr., ix, 1907.

certain phenomena connected with direct and indirect vision, visual acuity and the visual sensations produced by shadows.

Direct and Indirect Vision.—Under ordinary conditions, the fixation of an object is accomplished by turning our eyes in such a direction that its central area is brought to a focus upon the fovea centralis of the yellow spot. The line uniting these two points constitutes the line of most distinct vision, and is known as the *visual axis of the eye*. Thus, in mapping out the details of a certain visual field, we invariably direct our eyes first to one object or a part thereof, and then to another. Only that object gives a perfectly clear impression at any one time which projects its ray of light along the visual line directly into the

FIG. 441.—DIAGRAM OF A SECTION THROUGH THE FOVEA CENTRALIS. (The outlines of this figure have been traced from a photograph.) Magnified 350 diameters. (From a preparation by C. H. Golding-Bird.)

2, Ganglionic layer; 4, inner nuclear; 6, outer nuclear layer, the cone-fibers forming the so-called external fibrous layer; 7, cones; *m.l.e.*, membrana limitans externa; *m.l.i.*, membrana limitans interna.

fovea. Meanwhile, the other objects of this particular field appear less distinct, because the rays emitted by them, form too great an angle with the visual line and fall, therefore, upon the outlying regions of the retina, where vision is less acute. In reading we invariably fix one word after another. Quite similarly, it will be noticed that if we gaze at a single word upon a page, the other words remain indistinct and the more so, the greater the distance between them and the one brought to a precise focus upon the fovea. The imaginary lines which connect the outlying luminous points of an object with the more peripheral elements of the retina, constitute *secondary visual axes*. It will

be seen, therefore, that the visual appreciation of our external world is accomplished by *direct* and *indirect vision*. The former leads to the formation of an image in the fovea, and the latter to the formation of an image upon the more outlying districts of the retina.

This discussion clearly shows that the visual axis and the optical axis of the eye are two distinct factors. The former is the imaginary line along which the most distinct vision is obtained, because it connects the object with the most sensitive area of the retina, the fovea centralis of the yellow spot. The latter is the line of most perfect refraction, because the different refractive media of the eye are centered upon it. The most ideal system, of course, is the one in which the refractive media are adjusted in such a way that their central rays are brought to a precise focus upon the most sensitive region of the receptor. This is true of the photographic camera, but not of the human eye, because the latter frequently shows a divergence of its visual and optical axes of from 3.5 to 7 degrees.

Visual Acuity.—Another argument in favor of the view that the cones are the most important element in vision is presented by the close correspondence between the smallest possible image and the disposition of the cones in the fovea. Salzer¹ has shown that 0.01 mm². of fovea contains 138 cones, and that an illuminated sheet is perceived as such only if each cone is the recipient of at least one ray of light. This necessitates about 140 rays for each 0.01 mm². of foveal surface. In order to obtain a mosaic impression, the different cones must be invested by a zone of non-stimulated cones. C. DuBois-Reymond² has estimated the number of rays then required at 72 per 0.01 mm². of foveal surface. Thus, a double star is recognized as two distinct bodies only if the distance between them corresponds to a visual angle of 60 seconds. Quite similarly, two white lines drawn across a black surface, are perceived as two lines only if the distance between them subtends a visual angle of 64 to 73 seconds. At these angles, the image covers an area of 0.0045 to 0.0055 mm². of retina and involves, therefore, two cones of the fovea. These experiments also show that the visual acuity does not differ greatly within the fovea, and especially not within the foveola. Outside the fovea, however, the acuity diminishes very rapidly, and already at a distance of 20 degrees, the lines of the image must be separated by a distance of 0.035 mm. in order to produce separate impressions.

Guillery has estimated the size of the smallest perceptible image at 0.0035 mm²., this value being applicable only to the center of the fovea, i.e., to the foveola. For this determination he employed a black dot upon a white background which was gradually moved away from the eye until it just barely disappeared. When thus just barely producing a retinal stimulation, the size of the image may be calculated by correlating its distance from the eyes with its diameter. Inde-

¹ Dissertation, Berlin, 1881.

² Zeitschr. für Psych. und Physiol. der Sinnesorgane, xii, 1896, 243.

terminations of this kind, it is important to have a uniform and moderate intensity of illumination, because visual discrimination markedly increases with the light until a certain upper limit has been reached.

Purkinje's Figures.—The fact that the sensory elements of the retina are deeply seated, is also proved by the phenomenon commonly known as "Purkinje's images."¹ It has been pointed out that the blood-vessels of the retina ramify upon its inner surface, whereas the rods and cones constitute its outermost layer. Consequently, it might be supposed that all light entering the eye must cast a shadow of the blood-vessels upon these sensitive elements. Actually, however, a disturbance of this kind is obviated by the fact that the diameter of even the largest retinal vessel amounts to only one-sixth of the thickness of the retina, while the diameter of the pupil equals only about one-fifth of the distance between this orifice and the fundus. Under ordinary conditions, therefore, the rods and cones are the recipients of the penumbra of the blood-vessels, while their umbra falls upon the inner layers of the retina. Experimentally, however, we can make use of two or three different means to render them visible by throwing their shadows upon parts of the retina not ordinarily exposed by them.

If the eye is turned inward and is directed upon a dull background while the attendant reflects a beam of light upon the outer surface of the sclera directly behind the cornea, an arborescent image of the blood-vessels of the illuminated part of the eyeball will be obtained (Fig. 442). In this case, blood-vessel *B* throws a shadow upon the neighboring retina opposite the beam of light *AB*. If the latter is then moved one way or another, the image of these vessels is shifted in the same direction. Naturally, this stimulation at *C* is projected into space through the optical axis as apparently having come from *D*. This method may also be employed to calculate the distance between the blood-vessels and the sensory elements of the retina, the factors necessary for this calculation being the distance of the background from the eye, the dimensions of the eyeball, the angle through which the light is moved, and the apparent movement of the image upon the screen. The values obtained in this way vary between 0.17 and 0.36 mm. Since it has been determined by histological measurements that the rods and cones lie at a distance of from 0.2 to 0.3 mm. below the blood-vessels, we have every reason to suppose that the rays of light are received by these particular constituents of the retina.

FIG. 442.—DIAGRAM TO ILLUSTRATE PURKINJE'S FIGURES.

A, source of light; *B*, blood-vessel; *C*, shadow thrown by it, which stimulation is projected to *D* upon the screen.

¹ Beitr. zur Kenntniss des Sehens, Prag, 1819.

The retinal blood-vessels may also be rendered visible by moving a candle to and fro in front of the eye while gazing upon a dark background. In accordance with the foregoing discussion, it will be seen, however, that the candle must be held well to one side of the visual line, otherwise the shadows of the vessels cannot be made to fall upon a lateral zone of the retina which is ordinarily not exposed to the stimulation by these vessels.

A third method consists in permitting a beam of light to enter through a pin-hole in a cardboard held directly in front of the cornea. In this way, sharply defined shadows of the blood-vessels will be thrown upon the underlying rods and cones, but even now it is necessary to move the cardboard rapidly to and fro in front of the eye, so that the shadows are not allowed to rest upon the same area of the retina for any length of time.

Chemical and Physical Changes in the Retina on Stimulation by Light.—Having established the fact that the rods and cones are the elements which are most directly concerned with the transformation of the light stimulus into a visual impulse, we are now in a position to study the manner in which their stimulation is brought about. The theories pertaining to this subject may be classified as follows:

1. *Mechanical imprint theory* which holds that the rays of light produce impressions upon the retina, similar to those resulting when the tips of the fingers are made to impinge upon a layer of gelatin.

2. *Thermal theory* which proposes that the rays of light traversing the retinal elements, generate heat.

3. *Electrical theory* which suggests that the waves of light are transformed into electrical energy.

4. *Chemical imprint theory* which holds that the rays of light give rise to chemical reductions, the retina containing the phototropic substances necessary for the formation of this imprint.

Though in the present state of our knowledge no absolutely convincing proof can be furnished for any one of these conceptions, the chemical imprint theory is by far the most satisfactory, because we are in possession of certain evidence tending to support it. In analogy with the sensitive plate used in photography, it is assumed that the retina contains a phototropic substance which is dissociated by the entering rays of light. The question may then be asked, whether such a substance has actually been isolated. It will be remembered that the outer poles of the rods and cones are situated upon a layer of pigment which has its origin in the adjoining hexagonal cells of the choroid-retinal junction. This pigment possesses a reddish color in amphibia, and a violet color in fish, owls, sheep, and man.¹ For this reason it is commonly known as *visual purple* or *rhodopsin*. In 1876 Boll² made the interesting observation that this formed pigment does not remain stationary, but moves in and out of the aforesaid cellular

¹ H. Müller, *Zeitschr. für wissensch. Zoologie*, iii, 1851, 234.

² *Sitzungsber., Akad. der Wissensch., Berlin*, 1876.

receptacles along definite channels. It is true, however, that the latter is chiefly associated with the rods and is absent in the fovea centralis which is wholly composed of cones. Since we shall have occasion to refer to this point again later on, it suffices at this time to note that a dark adapted eye presents a sharply defined basement layer of pigment, while a light adapted eye shows a dissemination of this pigment in between the rods so that their outer poles are thoroughly invested by it¹ (Fig. 443). Secondly, it has been observed by Stort² that the cones are contractile and move outward under the influence of light. Thus, the dark adapted eye contains these elements

FIG. 443.—SECTION OF FROG'S RETINA SHOWING THE ACTION OF LIGHT UPON THE PIGMENT-CELLS, AND UPON THE RODS AND CONES. HIGHLY MAGNIFIED. (v. Gendren-Stort.)

A, From a frog which had been kept in the dark for some hours before death. B, from a frog which had been exposed to light just before being killed. Three pigment-cells are shown in each section. In A the pigment is collected towards the body of the cell; in B it extends nearly to the bases of the rods. In A the rods, outer segments, were colored red (the detached one green); in B they had become bleached. In A the cones, which in the frog are much smaller than the rods, are mostly elongated; in B they are all contracted.

in a position next to the pigment layer and retracted in between the neighboring rods, while the light adapted eye shows them in close relation with the membrana limitans externa.

These changes may be demonstrated very easily in the eyes of frogs which have been kept for some time in the dark or have been exposed to strong daylight. After its removal the eye is quickly bisected equatorially and placed in a fixing solution and subjected to the ordinary histological processes. In the normal eye, the visual purple can only be seen in fish, because the layer of the rods and cones is here situated upon a white tapetum. In man, on the other hand, the

¹ Kühne, Untersuchungen aus dem physiol. Institut zu Heidelberg, 1878.

² Oudezock, Physiol. Labor., Utrecht, ix, 145.

ophthalmoscope is of no avail, because the perfectly clear retina lies here upon the dark background of the choroid. Various other means, however, are at our disposal to show that this pigment is a chemical entity serving a particular purpose. Thus, it will be found that the retina of an eye which has been protected against light for some time, possesses a purple color, while one which has been exposed to strong daylight, is entirely colorless. The purple color of the former soon becomes yellowish and then disappears completely. This *bleaching property* of the visual purple enables us to employ the retina in the manner of a photographic plate, but naturally, the objects to be taken must show sharp contrasts. Most commonly, we employ the eye of a rabbit or frog which has been directed for a brief period of time toward a window, preferably one with many cross-bars. It is then bisected and immersed in a 4 per cent. solution of alum which temporarily fixes this inverted image of the window. A retinal photograph of this kind is known as an *optogram* (Fig. 444).

FIG. 444.—OPTOGRAM IN EYE OF RABBIT.

1. The normal appearance of the retina in the rabbit's eye: *a*, The entrance of the optic nerve; *b, b*, a colorless strip of medullated nerve fibers; *c*, a strip of deeper color separating the lighter upper from the more heavily pigmented lower portion. 2 shows the optogram of a window. (Howell.)

It has previously been mentioned that the visual purple is protruded from the pigmental epithelium in the form of delicate processes which invade the layer of the rods and cones and closely invest the outer limbs of the former. It cannot surprise us, therefore, to find that the retina of the light adapted eye is closely adherent to the choroid, while that of the dark adapted eye may be easily peeled off. Furthermore, a retina which has been bleached, does not regain its original color unless it is allowed to remain in contact with the pigmented epithelium. These data clearly prove that the choroidal pigment serves as the mother-substance of the visual purple, its function being to supply this sensitive substance to the outer limbs of the rods as quickly as it is reduced by the light rays.

The *visual purple* may be extracted from the retina by means of solutions of bile salts. It will be remembered that the latter possess the power of quickly abstracting the hemoglobin from the red blood corpuscles. These actions are very similar, in the present case the visual pigment being liberated from its combination in the rods. The

solutions thus obtained, contain the visual purple in its original form and may be bleached by exposing them to light. It does not seem likely, however, that this reduction gives rise to distinct bodies, such as have been designated by Kühne as visual yellow and visual white.¹ A dissolution of this pigment results in alkalies, alcohol, ether, chloroform and most acids. It is resistant against ammonia, sodium chlorid, benzol, fats and oils. Even the different rays of the spectrum affect it in an unequal measure, red and orange being least destructive and yellow and green most destructive.

The Function of the Visual Purple.—While it is perfectly obvious that the visual purple is an unstable pigment which is decomposed by the ethereal impacts, this fact does not furnish an adequate explanation for the changes resulting in the rods and cones in consequence of the vibratory energy imparted to them by the ether waves. Neither is it possible to recognize in this pigment a substance which is absolutely essential to vision, because it is absent in some animals, such as the pigeon, hen, certain reptiles, and bats, and remains wholly confined to the rods. Consequently, since the fovea centralis is composed exclusively of cones, it is absent from this area which, admittedly, is the place of most acute vision.

These discrepancies force us to assume that the visual purple serves merely as a sensitizing substance which is made use of chiefly in low intensities of light. It is a well-known fact that the sensitiveness of the fovea decreases in dim light, while that of the peripheral expanse of the retina increases. In other words, while the cones are employed in day-vision, the rods are brought into more general use in low intensities of light. In semi-darkness, therefore, we invariably endeavor to bring the image into the peripheral retinal field by slightly diverging the eyes, while in daytime we focalize the object directly upon the yellow spot. This shows first of all that the cones themselves are sensitive to light and need no sensitizing substance in ordinary light. Their acuity, however, decreases steadily with the intensity of the light, just because they are devoid of this pigment. For this reason, therefore, the yellow spot becomes practically blind in semi-darkness. By analogy, it may then be concluded that the greater sensitiveness of the peripheral zone of the retina in the dark-adapted eye is directly dependent upon the production of the visual purple and its movement to the outer segments of the rods. By virtue of this pigment, these elements are enabled to raise the otherwise inert light rays above the threshold of stimulation. In this connection, brief reference should also be made to the view of von Kries,² according to which the perception of color is distinctly a function of the cones, while the rods are regarded merely as playing a part in the perception of white light of

¹ Abellsdorff and Köttgen, *Zeitschr. für Psychol. und Physiol. der Sinnesorgane*, xii, 1896.

² *Zeitschr. für Psychol. und Physiol. der Sinnesorgane*, ix, 1895, 81.

low intensity. This theory will be more fully discussed later on in connection with color-vision.

Phosphenes.—It has been emphasized repeatedly that the adequate stimulus for the retina is the light ray, because this receptor presents the most favorable conditions for the transformation of this form of energy into nerve impulses.¹ In a slight measure, however, the retina is also accessible to inadequate stimuli in the form of mechanical and electrical impacts, but the visual impressions then obtained retain the character of very general sensations of light. These sensations are of course subjective in their quality, because they are not caused by homologous stimuli of light, but by stimuli of a heterologous kind. Thus, if the eyelids are closed and

FIG. 445.—DIAGRAM TO ILLUSTRATE THE PHENOMENON OF PHOSPHENES.

S, The mechanical stimulation of the coats of the eye ball at *s* gives rise to a sensation of light which is projected to *i* in the opposite visual field.

the eyes are turned inward, any pressure upon the external part of the eyeball, such as may be exerted with the blunt end of a pencil, gives rise to luminous sensations, known as "phosphenes" (Fig. 445). In this particular case, they appear in the form of bright yellowish rings, each surrounding a dark center. It is to be noted especially that this sensation, although evoked at the point of pressure, is referred to the opposite visual field. In other words, any pressure exerted upon the outer zone of the eyeball gives rise to a sensation which is projected into the nasal area of the visual field, because under ordinary conditions the outer retina is stimulated by objects situated in the nasal field. A phosphene of similar character may be produced by gazing into a bright light while the eyes are rapidly moved from side to side. Inasmuch as the eyeball is relatively fixed at the point where the optic nerve leaves it, this abrupt lateral deviation gives rise to a mechanical stimulation of the retinal elements situated around the edge of the optic disc. In this case, the visual sensation is projected directly outward into the central visual field. Phosphenes also result in consequence of stagnation at the points of exit of the *venæ vorticosæ* and in consequence of the pulsations of the retinal arteries. They are most intense in conditions of hyper-excitability of the general nervous system.

Electrical Variations in the Eye on Vision.—The retina shows a current of rest or injury as well as a current of action. If an excised eye is connected with a galvanometer by two non-polarizable electrodes, one of which is adjusted to the cornea and the other to the end of the optic nerve, the latter is galvanometrically negative to the former.

¹ Klein, *Archiv für Physiol.*, 1910, 531. The phenomenon of the phosphenes has been known since the time of Aristotle.

This variation is the ordinary current of injury caused by the cutting of the optic nerve. At this time, however, this nerve is galvanometrically positive to the lateral zones of the fundus of the eyeball.¹ Like all living tissues, the retina also becomes the seat of electrical variations when stimulated. Thus, the falling of light into a dark-adapted eye gives rise to an electrical change which may be regarded as analogous to the current of action of any motor or sensory nerve.² While the nature of this response is greatly dependent upon the strength and duration of the stimulus, and the condition of the eye, it generally results after a latent period of not more than 0.01 second.³ Its direction is the same as that of the preëxisting current of injury, provided the electrodes have been applied in the same manner as before. Consequently, since it passes from the fundus to the cornea and thus merely intensifies the current of injury, it forms a positive variation. This is succeeded by a gradual diminution and later on by a second prolonged increase. Einthoven and Jolly⁴ who have analyzed this current with the aid of the string galvanometer, endeavor to explain its unusual complexity by assuming the occurrence in the retina of three distinct processes, called *A*, *B* and *C*. The first develops more rapidly than the other two and is especially marked in a light-adapted eye. When this eye is stimulated, it gives rise to a negative and when darkened, to a positive potential difference. The second process is less speedily initiated, and leads to a positive variation on stimulation and a negative difference on darkening. This process is brought into play with greatest intensity in a dark-adapted eye, when it is illuminated with a moderate light. The third process yields the same results as the second, but its speed of development is much slower. It is not initiated in a light-adapted eye.

When the non-polarizable electrodes are adjusted to the longitudinal and cut surfaces of the optic nerve itself, a simple negative variation is obtained, presenting the same characteristics as the ordinary action current of nerve. Peculiarly enough, however, this variation is evoked not only when the light is flashed into the eye, but also when it is withdrawn. Photo-electrical phenomena have also been observed in plants when alternately darkened and lightened.⁵

¹ Holmgren, *Zentralbl. für Physiol.*, xi, 1897.

² Gotch, *Jour. of Physiol.*, xxxi, 1904, 31.

³ Nagel, *Handb. der Physiol.*, 1905, iii, 103.

⁴ *Quart. Jour. of Exp. Physiol.*, i, 1908, 373.

⁵ Waller, *Proc. Royal Soc., London*, lxvii, 1900.

CHAPTER LXXII

THE FORMATION OF THE IMAGE UPON THE RETINA

The Reduced or Schematic Eye.—The eye consists of two parts, namely, the hemispherically expanded retina with its mosaically arranged sensory elements and a number of adjuncts which form a dioptric mechanism for projecting the light rays upon this receptor. Having previously studied the structure and function of these parts separately, we are now in a more favorable position to deal with them collectively and to see how they are capable of forming a real image of external objects in their correct spatial relationships upon the retinal surface. This analysis should not be attended by undue difficulties, because it is based essentially upon the data pertaining to the refraction by biconvex lenses given in one of the preceding chapters.

The normal or emmetropic eye is constructed in such a way that the different rays of light are brought to a precise focus upon the retina.

FIG. 446.—DIAGRAM TO ILLUSTRATE THE POSITION OF THE CHIEF POINTS OF REFRACTION IN OUR EYE.

A, Cornea; B, anterior surface of lens; C, posterior surface of lens.

This refraction, however, involves not only those rays which pursue a course parallel to its visual axis, but also those which are projected toward it in a divergent direction and would otherwise be lost to it. This power it exerts by virtue of its ability to accommodate for near and far objects. But while the process of refraction in our eye is essentially the same as that exhibited by biconvex lenses, the fact that several media take part in it, tends to make matters more difficult. A biconvex

lens changes the course of the ray in two places, namely, at the point where the latter enters the denser medium and again where it leaves it. Upon its passing from the rarer into the denser medium it is refracted toward the perpendicular, and upon its passing from the denser into the rarer medium, away from the perpendicular. Our eye contains a large number of these points of refraction, chief among which are the anterior surface of the cornea and aqueous humor, the anterior and posterior surfaces of the lens, together with the anterior surface of the vitreous humor (Fig. 446). In fact, the entering ray of light first meets with a layer of tears, the refractive power of which is considerable. Inside the cornea it is not deviated very materially, because the anterior and posterior surfaces of this medium are

practically parallel, while the refractive power of the tears and aqueous humor are nearly equal. It is strongly deviated, however, at the anterior and posterior surfaces of the lens, because the refractive indices of the aqueous and vitreous humors are less than that of the lens. In general, the refractive power of this entire system may be calculated without difficulty, provided the following factors are open to analysis:

- (a) The indices of refraction of the different media.
- (b) The radii of the different curved surfaces.
- (c) The distances between them.

Regarding the first factor, the following values have been obtained:¹

Air.....	1.0	
Cornea.....	1.3771	
Aqueous humor.....	1.3374	
Lens { Capsule	1.3599	} 1.4371
Ext. layer.....	1.3880	
Body.....	1.4107	
Vitreous humor.....	1.3360	

It will be seen that the indices of the aqueous and vitreous humors are practically the same and correspond to that of water. Furthermore, it will be observed that the total refractive power of the lens (1.4371) is greater than that of its different layers, as well as of that of its body. This apparent discrepancy is explained by the fact that its central substance, when isolated, possesses a greater curvature than its entire mass and, therefore, gives rise to a stronger refraction in relation to its index.

In order to simplify matters Listing² has combined these different refractive media into a single one possessing a general refractive index of 1.33. If united in this manner, the entire eye may be regarded as being composed of a homogeneous substance presenting to the air a single convex surface with a refractive index of 1.33, and a radius of curvature of 5.017 mm. (Fig. 447). The principal point of the refracting surface of this reduced or schematic eye lies 2.1 mm. behind the anterior surface of the cornea, and its nodal point (*N*) or optical center 0.04 mm. in front of the posterior surface of the lens, *i.e.*, 7.3 mm. behind the anterior surface of the cornea. The principal focus of this imaginary refracting surface lies 22.2 mm. behind the anterior surface of the cornea of the actual eye. The optical power of this

FIG. 447.—DIAGRAM TO ILLUSTRATE THE REDUCED OR SCHEMATIC EYE.

R, imaginary refracting surface;
N, nodal point of this system.

¹ Matthiessen, Pflüger's Archiv, xxxvi, 1885.

² Wagner's Handwörterbuch der Physiol., 1853, iv, 451.

reduced system is 50.8 diopters, and hence, the focal point of this eye, when accommodated for a far object and in the position of rest, lies precisely upon the retina.

The Formation of the Retinal Image.—In reducing the eye into this simple form, Listing has followed the mathematical expositions of Gauss ¹ which show that the several media of any refractive system, whenever centered upon the same optical axis, may be considered as forming two parallel planes possessing an equal refractive power (Fig. 448). For practical purposes, these two planes (P) with their respective nodal points (N) may be regarded as being coincident, because the distance between them is actually very small so that the refracted ray from the first plane is sent into the second still parallel to the optical axis. In constructing the image of object AB , it must be remembered that any luminous point upon AB sends out two rays, one of which passes through the nodal point unrefracted, while the

FIG. 448.—DIAGRAM TO SHOW THE INVERSION OF THE IMAGE BY PARALLEL REFRACTING SURFACES.

AB , object; $A'B'$, image; N , nodal point of two parallel refracting surfaces P ; F , focal point.

FIG. 449.—DIAGRAM TO ILLUSTRATE THE CONSTRUCTION NECESSARY TO DETERMINE THE LOCATION AND SIZE OF THE RETINAL IMAGE.

other pursues a course parallel to the optical axis of this system and is then refracted through its focal point F . At the point of intersection of these two rays (A^1) lies the image of luminous point A . If this construction is repeated for luminous point B , it will be seen that the image of AB is inverted.

The same construction may be followed in the reduced eye (Fig. 449), because we know the center of curvature (n) of its single imaginary refracting surface (R), in other words, its nodal point through which all the principal rays may be imagined to enter the eye. These rays are not deviated from their course, owing to the fact that they strike the refracting surface at right angles. Consequently, all that is required for the determination of the position of the image of an object upon the retina, is to draw straight lines from its different luminous points through the nodal point n . It is evident that the retinal image is inverted and that its size will be the smaller, the less the distance of the nodal point from the retina and the greater its distance from the object. Expressed in terms of the visual angle, it may then be said

¹Dioptische Untersuchungen, Gesellsch. der Wissensch., Göttingen, 1838-1843.

that the image becomes the smaller, the less this angle. Obviously, the latter must vary directly with the size of the object and inversely as its distance. Thus, if we gaze first at the moon and then at a more distant but much larger fixed star, the visual angle formed by the rays from the moon is much larger, because its relative proximity to the eye more than makes up for its smaller size.

This inversion of the image may be conveniently demonstrated by observing a landscape upon the ground glass of a photographic camera. Quite similarly, we may employ the eye of an albino rabbit which contains no choroidal pigment and in which, therefore, the image may be seen through the transparent sclerotic coat. The question may then be asked, why do we not perceive objects upside down? Our correct interpretation of spatial relationships is gained in the course of time by experience and in consequence of the association of various sensory impressions. In other words, our psychic mechanism is adjusted in such a way that it conforms absolutely to this inversion of the image. Consequently, any ray of light striking the retina below, is invariably regarded as having arisen from a luminous point situated in the upper visual field. Quite similarly, any stimulation of the upper expanse of the retina is correctly interpreted as having originated in the lower visual field, and so on.

The fixed character of our spatial associations may be proved in different ways. Thus, we have previously observed that the mechanical stimulation of the retina gives rise to luminous sensations or phosphenes, which are invariably referred to the visual field opposite the seat of the stimulation. The reason for this is that these elements are invariably stimulated by rays which are projected along these particular secondary lines. In localizing these retinal stimuli in space, it may be imagined that we are guided by the local signs previously established by them in the visual center. Like the receptors of the skin, each retinal element may be assumed to be connected with a particular central neurone which in the course of time has become adapted to a perfectly definite sensation. Our psychic interpretation, therefore, corresponds, as it were, to a reversal of the rays of light, *i.e.*, the stimulated points upon the retina may be imagined to emit rays which pass in a straight line through the nodal point and form an imaginary image in space in accordance with their secondary axes.

Another good illustration of this general fact is obtained whenever objects are held so close to the eye that the ordinary inverted image must give way to an erect shadow (Fig. 450). To accomplish this end, a card with a pin-hole is held at a distance of about 3 cm. in front of the eye, *i.e.*, within the near point of vision. If a pin is now moved slowly upward in front of the pupil and as close as possible to the cornea, the pin appears to enter the visual field from above. The same result is obtained if the object is moved along any other meridian of the cornea. Since the pin-hole lies inside the near point of this eye, it is converted into a source of light which widely illuminates the ret-

ina. Inside this circle of light upon the retina lies the shadow of the pin in its natural position. It appears inverted for the obvious reason that the retinal elements stimulated by this shadow, are associated in an inverse manner. Consequently, any shadow falling upon the lower expanse of the retina, is interpreted as having been produced by an object situated in the upper visual field.

FIG. 450.—DIAGRAM TO ILLUSTRATE THE FORMATION AND PROJECTION OF THE SHADOW OF A PIN.

A, Pin; J, shadow of it upon lower retina; P, projected as if moving into the visual line from above.

The Size of the Retinal Image.—The dimensions of the image of an object upon the retina may readily be ascertained if the size of the object and its distance from the cornea are known (Fig. 451). Supposing that the object AB is focused upon the retina in $A'B'$, then AB and $A'B'$ really form the bases of two similar triangles, the apices of which are situated at the nodal point of the lens, while its sides are formed by the secondary axes AB' and BA' . If C stands for the distance of the nodal point from A , and D for the distance of this point from B' , then:

$$\frac{AB}{C} = \frac{A'B'}{D}$$

FIG. 451.—DIAGRAM TO SHOW HOW THE SIZE OF THE RETINAL IMAGE MAY BE DETERMINED.

As has been stated above, the distance of the image from the nodal point may be reckoned at about 15 mm. Consequently, an object 120 feet in height, placed at a distance of 25 miles, forms an image upon the retina, the dimension of which is

$$\frac{120 \text{ ft.}}{25 \text{ miles}} \times 15 \text{ mm.}, \text{ i.e. } \frac{120 \text{ ft.}}{5280 \times 25 \text{ ft.}} \times 15 \text{ mm.}, \text{ or } \frac{1}{1100} \times 15 \text{ mm.} = 0.013 \text{ mm.}$$

This image, therefore, would scarcely equal the diameters of two red corpuscles and would cover about four cones of the fovea centralis. This same object placed at a distance of one mile (5280 feet), would give an image measuring 0.341 mm. in height, which corresponds to about the diameter of the fovea centralis.

The Visual Field. Perimetry.—If our attention is called to an object, our eyes are always turned in such a way that its central area is brought to a precise focal point in the foveæ centrales. This act constitutes direct vision. At this very time all other objects in space fall upon the outlying districts of the retina and are therefore seen by indirect vision. Direct vision, therefore, is effected through the visual axis, connecting the object with the fovea, and indirect vision through secondary axes which fall upon the more peripheral zones of the retina. Both eyes together cover a certain extent of the external world which is known as the visual field, but this entire field is really made up of two, a right and a left, the nasal spheres of which overlap. From what has been said above regarding the manner of refraction in our eye, it must be evident that the retinal image is inverted and that objects situated in the upper extent of the visual field, are centered upon the lower half of the retina, and *vice versa*. The same is true of objects situated respectively in the right and left halves of the visual fields, because they fall upon the opposite side of the retina.

The configuration of the entire visual field, as well as of that of each eye, depends chiefly upon the anatomical characteristics of the margins of the orbital cavity. Centrally, each field is restricted by the bridge of the nose, above by the orbital arch, and below by the cheeks. Consequently, each field really presents an irregular oval outline, instead of a circular one which it would possess if the eye were protruded beyond these restricting boundaries. Its limits may be ascertained by steadily gazing with one eye upon a mark upon a large cardboard, placed at a distance of about 25 cm. vertically in front of the cornea. The visual axis of this eye should strike the cardboard exactly at right angles. A small object is then moved from without along the vertical, horizontal and oblique meridians as charted upon the cardboard. A mark is made each time when the observed person obtains a clear impression of this object. If these outlying points are then joined with one another, we obtain the boundaries of the visual field of this particular eye at the distance of 25 cm.

An instrument commonly made use of for mapping out the visual field is the perimeter. The one devised by Aubert and Forster¹ (Fig. 452), consists of a hemispherical band of metal fastened to a stand and movable so as to cover the different meridians of the eye. In front of this arc is placed a support for the chin of the observed person, his eye being adjusted in such a way that he is able to gaze horizontally at a white object fastened to the center of this circle (Fig. 452). A small white disc is then moved slowly from without along this arc until it becomes clearly visible. The arc is graduated, allowing the moment of the appearance of this object to be charted (Fig. 453). This procedure is repeated along the

¹ Archiv für Ophthalmologie, iii, 1857.

other meridians until the boundaries of the entire visual field have been accurately mapped out.¹

Clinically this instrument is employed for determining the seat of lesions of the retina or of the optic tract and visual center. Obviously, any defect of the optic path must give rise to a retinal area of indifference and hence, to a dark zone within the visual field. Thus, it will be remembered that unilateral lesions of the occipital cortex give rise to the condition of hemianopia or half-blindness of the retina on the corresponding side. If their right halves have in this way been rendered functionally useless, the left halves of the visual fields are blotted out. Direct vision, however, is retained, because each fovea centralis is connected with both

FIG. 452.—THE PERIMETER.

occipital centers. Very similar defects in the visual field follow injuries to the optical tract or to the retina itself. Thus, the occlusion or rupture of a terminal branch of the retinal artery most generally leads to a uselessness of a circumscribed patch of the retina with a corresponding defect in the visual field of this eye. This defect, however, cannot become apparent unless the corresponding area of the opposite retina has also been injured. Admittedly, the two retinae act in unison and compensate for minor defects so long as the injury remains confined to one of them. This functional reciprocity has already been fully discussed in the paragraphs dealing with the blind spot. It was then found that while a certain number of the rays

¹ Peter, *Principles and Practice of Perimetry*, New York, 1916.

emitted by an object, are always projected upon the blind spot of one eye, this defect is overcome in binocular vision by the fact that the corresponding rays in the opposite eye are focalized outside this area and are therefore able to produce a precise and complete impression in consciousness.

Since the sensitiveness of the retina diminishes steadily from center to periphery and also shows certain minor fluctuations in different persons, it cannot surprise us to find that the visual field frequently possesses marked irregularities. Furthermore, it must be evident that the luminosity and color of an object have much to do with its size, because a white disc invariably yields a larger field than

FIG. 453.—PERIMETER CHART TO SHOW THE FIELD OF VISION FOR A RIGHT EYE WHEN KEPT IN A FIXED POSITION.

one poorly illuminated or colored. Consequently, definite conclusions regarding abnormalities of the visual field can only be drawn from a perimetric chart which has been obtained under test conditions.

CHAPTER LXXIII

ABNORMALITIES IN THE REFRACTION OF THE EYE

Constant Optical Defects of the Eye.—In a perfect dioptric system the media are absolutely transparent. This is not the case in the human eye, because if a strong beam of light is thrown into its pupil, the light is diffused by the different luminous points of its refractive media. In fact, in many instances true opacities may be detected which are dependent upon the presence of formed elements within the

vitreous humor. In order to render the latter visible, the eye should be turned upward upon a uniformly illuminated surface, when they will place themselves directly in the line of vision, and give rise to a sensation of beads, strings or patches floating through the visual field. On account of their almost constant motion, which may be increased by movements of the head or eyes, they are known as the *muscae volitantes*. They are said to represent the remains of the embryonic structure of the vitreous humor, such as cells which have failed to undergo a complete transformation into vitreous substance. These fleeting visual sensations belong to the group of the *entoptic phenomena*, because they are produced by objects within the eye.

The human eye also shows an imperfect centration of its refractive media. In the horizontal meridian the optical axis of the cornea differs from that of the lens by 0.3° , and in the vertical meridian by as much as 1.3° . Furthermore, attention has already been called to the fact that the optical axis of the eye does not coincide exactly with the visual axis. Naturally, the most perfect system would be the one in which the refractive media are accurately centered upon an axis which strikes the retina in its most sensitive area.

Reference has already been made to the fact that the crystalline lens is not free from spherical aberration, the rays passing through its peripheral zone being converged more than those traversing its center. It is also open to chromatic aberration, the violet rays being brought to a focus in a point closer to the lens than the red rays. Like in all optical instruments, these aberrations are minimized by a stop in the form of the iris which shuts out its marginal zone. In spite of this fact, however, we still obtain a slight spherical aberration which, together with the imperfect centration of the refracting media, gives rise to a mild degree of astigmatism. Thus, a star or the light of a lantern is not seen as a round luminous point, but as beset with radial streamers. Quite similarly, the chromatic aberration still remaining, frequently amounts to 0.5 mm. as far as the violet and red rays are concerned. This condition, however, does not interfere appreciably with the clearness of the retinal image, at least, not with the impression produced by it in consciousness. Admittedly, the retina becomes abruptly insensitive toward the rays at the extreme ends of the spectrum, and is more readily excited by the rays in and near the yellow. Consequently, the absence of chromatic aberration in our eye is due to the fact that the iris prevents refraction through the peripheral zone of the lens, and secondly, to the physiological and not to the optical qualities of our eye.

Among these dioptric defects of our eye might also be mentioned the entoptic phenomena produced by the tears anointing the anterior surface of the cornea, as well as by the particles of mucus, globules of fat and dust contained therein. The latter are constantly removed from in front of the pupil by the movements of the eyelids. Subjective visual impressions also result in consequence of the heterologous

excitation of the retina by strong pulsations of the retinal blood-vessels, increased intraocular pressure, and venous stagnation caused, for example, by the acts of coughing and sneezing.

Inconstant Optical Defects of the Eye.—It is the purpose of the normal eye to bring rays of light to a sharp intersecting point upon the retina. An eye which accomplishes this end, is said to be emmetropic. This condition of normal refraction is designated as *emmetropia*. Conversely, any eye which is not capable of producing a precise focus, is said to be ametropic. This condition of abnormal refraction is known as *ametropia*. The causes underlying the latter may be arranged in the following order:

- (a) Imperfect curvature of the cornea, astigmatism.
- (b) Diminished elasticity of the lens, presbyopia.
- (c) Imperfect shape of the eyeball.
 - (1) Myopia, the eyeball is too long.
 - (2) Hypermetropia, the eyeball is too short.

The condition of presbyopia has been fully discussed in one of the preceding chapters and need not be considered again at this time. Furthermore, while astigmatism is ascribed in this outline to a faulty curvature of the cornea, we should not lose sight of the fact that this condition may also be caused by an imperfect curvature of the lens; in fact, even a so-called normal eye is not entirely free from astigmatism, due very largely to an improper centration of the constituents of the lens. Regarding the exciting causes of ametropia no perfectly definite statements can be made. The shape of the eyeball is *inherited* together with other biological characteristics; hence, all these conditions may be entirely beyond our power of preventing them. This is also true of those defects which arise later on in life in consequence of retrogressive changes, such as infiltrations, alterations in the intraocular pressure, and senile weaknesses of the coats of the eyeball. In the latter case, the eyeball becomes more pliable and adjusts itself more completely to the shape of the orbital cavity. In spite of this important element of inheritance, however, it cannot be denied that these defects may also be *acquired* in consequence of an improper mode of living, and erroneous methods in the use of the eyes. Thus, the inhabitants in cities are constantly subjected to near work; their horizon being limited in many cases by the walls of the houses on the opposite side of the street. Besides, their daily work requires strong convergence of the visual axes which in itself heightens the intraocular pressure. The contrary picture is presented by the inhabitant of the open country whose visual impressions are in large part received from distances greater than 50 m., *i.e.*, from distances which require no accommodation at all. Civilization imposes upon us many conditions which can only be met by carefully following the most fundamental rules regarding physiological optics.

Astigmatism.—In accordance with perfect refraction, the cornea should form a section of a true sphere, but this is not always the case,

because slight differences between the curvatures of its vertical and horizontal meridians are not uncommon. Most generally, however, this defect is overcome functionally, so that an appreciable disturbance in vision can only result when these differences exceed a certain physiological limit. Astigmatism is classified as *regular* and *irregular*, the former term being applied to it when the meridian of maximal curvature lies at right angles to that of minimal curvature. Accordingly, irregular astigmatism may be defined as an improper curvature of the cornea along meridians which do not lie at right angles to each other. This variety is most commonly produced by an injury and subsequent formation of a scar in the course of a single meridian; hence, it is restricted to a relatively narrow region of the cornea. We also make use of the terms "*with the rule*" and "*against the rule*" astigmatism. The

FIG. 454.—DIAGRAM TO ILLUSTRATE THE CORNEA OF THE RAYS IN "WITH THE RULE" ASTIGMATISM.

AB, being the plane of greater curvature, its rays are brought to a focus nearer the lens than those traversing plane CD.

former implies that the cornea is more highly curved along its vertical meridian, while the latter signifies that its horizontal curvature is greater than its vertical. Ordinarily, astigmatism is of the regular variety, presenting itself, therefore, as an excessive curvature along its vertical plane.

The functional result of these corneal inequalities is not difficult to understand, if it is remembered that the more convex surface converges the rays of light more strongly than the less convex and hence, focalizes them more quickly than the flatter surface. We are dealing here with planes, *i.e.*, with linear refraction (Fig. 454). Consequently, an eye which has been rendered ametropic by "*with the rule*" astigmatism, converges those rays of light in a greater degree which traverse the vertical plane of its cornea (AB). Although the lens receives these rays in a more convergent form than those which have passed through the horizontal plane of the cornea (CB), it subjects both lines of light

rays to an equal degree of refraction. Accordingly, this eye obtains first of all an image of those rays which have traversed the more highly curved vertical meridian of the cornea (AB) and lastly, one of those rays which have passed through its relatively flat horizontal plane (CD). The first image (ab) must necessarily be a horizontal line and the second a vertical line (cd). In between these two images are

FIG. 455.—ASTIGMATIC CHART. (Howell.)

situated first a horizontal ellipse, then a circle and lastly, a vertical ellipse. The reason for this is that the rays ab again diverge distally to the horizontal image and henceforth intermingle with the still convergent rays cd .

To illustrate, let us fill a tall beaker with water, place it upon a table and project a round beam of light through its central area. The image is a vertical

FIGS. 456, 457.—LINES FOR THE DETECTION OF ASTIGMATISM.

line, because the column of water acts in the manner of a cylindrical lens, the greatest convexity of which is adjusted from side to side. If this beaker is now held horizontally so that its greatest convexity lies in the vertical plane, the linear image assumes a horizontal position. The same results may be obtained with a cylindrical lens. By means of two equally strong cylindrical lenses superimposed upon another at right angles, these linear lines may be reconverted into a rounded image.

The presence of astigmatism may be revealed by looking at a chart such as is represented in Fig. 455, because an astigmatic eye is unable simultaneously to obtain a perfectly clear image of lines placed at right angles to one another. An even more delicate test is presented by the concentric rings reproduced in Fig. 456. It should be emphasized, however, that the oscillating blurring effect which one frequently obtains while gazing at these charts, is not caused by an astigmatic condition of the refracting media of the eye, but by slight variations in the degree of contraction of the ciliary muscle. Such variations must necessarily give rise to changes in the accommodation.

FIG. 458.—OPHTHALMOMETER. (Hardy.)

An instrument which enables us to determine the direction as well as the degree of the excessive curvature of the cornea, is the *ophthalmometer* of Helmholtz (Fig. 458). It is constructed in such a way that the size and shape of the corneal image of any luminous object may be determined with absolute accuracy. Knowing the size of this object and its distance from the eye, as well as the size of the corneal reflection, it is possible to ascertain the radius of curvature of the cornea according to the equation $r = \frac{2pi}{o-2i}$. In this formula p represents the distance of the object from the cornea, o , the size of the object, and i , the size of the corneal image. It need scarcely be mentioned that the reflecting surface and telescope of this instrument may be rotated so as to enable the observer to measure the curvature of the other planes of the cornea and to compare them with one another. In the modern

instruments of this kind the luminous object, or target, is represented by a double figure possessing a sharp mathematical outline, which in turn is doubled by a prism. The four images thus obtained are first properly adjusted for a normal cornea. When transferred upon an abnormally curved cornea, this defect is made apparent immediately by their displacement toward one another.

The condition of astigmatism may be corrected in one of two ways: namely (a) by diminishing the refraction along the meridian of greatest curvature or (b) by increasing the refraction along the meridian of least curvature. Cylindrical lenses are used for this purpose, the refracting power of which compensates precisely for the unequal curvature of the cornea. In the former case we employ a lens designated as minus and, in the latter, one designated as plus.

Myopia.—The condition of myopia or near-sightedness is due either to an increase in the longitudinal diameter of the eyeball, or to an excessive refracting power of the lens and other media of the eye. In most instances, however, it is attributable to the former cause.

The increase in the length of the eyeball may amount to a fraction of a millimeter or to as much as 3.8 mm. Already with a lengthening

FIG. 459.—DIAGRAM TO ILLUSTRATE THE REFRACTION IN A MYOPIC EYE.

L , Luminous point focalized in L^1 in the vitreous humor. A concave lens L renders these rays more divergent so that they are made to intersect upon the retina in L^2 .

of 0.16 mm. the far point is moved to within 200 cm. from the eye, and with an increase of 3.8 mm. to within 10 cm. The near point is at this time only 5 to 6 cm. distant. Far objects, therefore, cannot be brought to a focus upon the retina, unless the eye is equipped with an artificial lens which exactly compensates for this defect. Thus, parallel rays emerging from so short a distance as 6 m., actually intersect in the vitreous humor in front of the retina. Distally to this point of intersection, the rays again diverge and strike the retina widely apart as a dispersion circle. It must be evident that this condition cannot be improved by accommodating more sharply, because any increase in the convexity of the lens must move the focal point farther toward the lens, and give rise to an even greater dispersion of the retinal image. Quite similarly, it may be reasoned that an object held very close to the eye, is in a much better position, because its

divergent rays are focalized far behind the lens and may, therefore, fall precisely upon the retina of the myopic eye.

In order to enable a myopic person to see distant objects clearly, we must lessen the convergence of the posterior bundle of the rays of light, *i.e.*, we must force their focal point farther backward until they reach the retina. How can this be done? By rendering the entering rays more divergent, so that they impinge upon the lens more widely separated from one another than formerly. The ordinary efforts of the ciliary muscle will then suffice to centralize these more divergent rays precisely upon the retina. Consequently, the condition of myopia necessitates the use of concave lenses of a diverging power exactly proportional to the degree of the myopia (Fig. 459).

Hypermetropia.—The condition of hypermetropia or far-sightedness is due either to a decrease in the longitudinal diameter of the eyeball or to a diminution in the refracting power of the lens and other media of the eye. The former is the most common cause. A hypermetropic eye is unable to focalize rays emitted by near objects, because its refractive mechanism is not sufficiently powerful to converge these rays in a way to bring them to a sharp intersecting point upon the retina. Since they are still too widely separated when they strike this receptor, they cannot give a clear visual impression. In the more severe cases, this statement also applies to the parallel rays, so that even distant objects cannot be seen distinctly when the eye is at rest. It is commonly said, that the focal point in the hypermetropic eye lies behind the retina, but naturally, this is only a theoretical possibility. With the increasing hypermetropia, the near point constantly moves farther away from the eye, sometimes as far as 200 cm., while its far point lies at an infinite distance.

It will be seen, therefore, that the hypermetropic, as well as the myopic eye, when at rest, sees distant objects indistinctly. Contrary to the myopic eye, however, the hypermetropic organ is able to overcome this difficulty for a time by constantly making extra efforts at accommodation. It is evident that any slight shortening of the eyeball may be compensated for by rendering the lens unusually convex, but naturally, these hyperefforts must fail to produce the desired result if the shortening has progressed beyond the limit of accommodation. Besides, these forceful contractions of the ciliary muscle are generally followed by a strained feeling, orbital pain, headache, and vertigo. Slight degrees of hypermetropia, however, may never be noticed for the reason that the person so affected may readily overcome them by a somewhat greater contraction of the ciliary muscle. In the course of time, this muscle then frequently undergoes a compensatory hypertrophy.

The condition of hypermetropia may be remedied by forcing the focal point farther toward the lens; *i.e.*, by rendering the rays of light emerging from the posterior surface of the lens, more convergent. How can this end be accomplished? By supplying the lens with

convergent rays of light, but since there are no convergent rays ordinarily available in space, this direction must first be imparted to the parallel and divergent rays by means of a convex lens (Fig. 460). The converging power of the lens interposed in front of the eye, must be proportional to the degree of the hypermetropia.

Keeping these facts clearly in mind, it will be seen that the condition of presbyopia developed in later years, must improve the vision of the myopic person, but diminish that of the hypermetropic. Obviously, the gradual flattening of the lens in consequence of the effects of old age reduces its refractive power and forces the focal point farther backward. If the eye is hypermetropic, the presbyopia makes matters worse, because it tends to move the focal point still farther "behind" the retina. In the myopic eye, on the other hand, a distinct improvement must result, because the presbyopic lens does not converge the rays so strongly, and hence, permits their focal

FIG. 460.—DIAGRAM TO ILLUSTRATE THE REFRACTION IN A HYPERMETROPIC EYE.

L , Luminous point focalized in L^1 "behind" the retina. A convex lens C renders these rays more convergent so they are made to intersect upon the retina in L^2 .

point to move closer to the retina. Conversely, a presbyopic eye may be greatly benefited by the subsequent development of a myopia, because the recession of the focal point is then compensated for by a displacement of the retina in a backward direction. These phenomena are generally designated as "second sight."

To summarize: An emmetropic eye (Fig. 461, E) brings parallel and even divergent rays of light to a sharp focus upon the retina, while a myopic eye (M) focalizes them in front and a hypermetropic eye, (H) "behind" the retina. In order to render M emmetropic, the entering rays of light must be diverged by means of a concave lens, while H can only be made emmetropic by converging them with the aid of a convex lens.

Simple Methods Used to Determine the Refractive Power of the Eye.—The acuity of vision may be tested in different ways. *Snel-len's test types* consist of a series of letters placed at a distance of 5 m. from the eye. It has been determined that the smallest object which a normal eye is capable of distinguishing at this distance, measures

1.454 mm. and that lines drawn from its two opposite poles through the nodal point of the lens, subtend an angle of 60 degrees. Consequently, any other two luminous points separated by a shorter distance than

FIG. 461.—DIAGRAM TO ILLUSTRATE THE REFRACTION IN EMMETROPIA AND AMETROPIA.

E, Emmetropic eye in which luminous point *L* is brought to a precise focus upon the retina, *L*¹; *M*, myopic eye in which *L* is focalized in front of the retina, *L*¹; *H*, hypermetropic eye in which *L* is focalized in *L*¹ "behind" the retina. In *M*, the use of a concave lens forces *L*¹ backward upon the retina, *L*², correcting the myopia, whereas in *H*, the use of a convex lens forces *L*¹ forward upon the retina, *L*².

the one just given, are no longer able to produce distinct impressions. At this distance, the retinal image measures 0.004 mm., which corresponds to a visual angle of 60 seconds. If smaller than this, the two

FIG. 462.—DIAGRAM TO ILLUSTRATE THE USE OF SNELLEN'S TEST TYPES.

focal points fail to give separate impressions, because they fall on one and the same cone. At a distance of 1 m., therefore, an object would have to possess a dimension of one-fifth of 1.454 mm., or 0.2908 mm.,

in order to subtend an angle of 60 seconds. Other letters may then be constructed for the intervening distances by simply multiplying the value of 0.2908 mm. by the distance (Fig. 462). This test, therefore, consists in determining the smallest retinal image, corresponding to a visual angle of 60 seconds, which an eye is capable of perceiving. If a person is unable to recognize this test type when held at its proper distance, he is first made to look at it through a weak convex lens. If this improves his vision, he is hypermetropic, because only an eye that is too short or possesses a subnormal power of refraction, is in a position properly to focalize convergent rays. He should be given the strongest convex lens with which he is able to see clearly, because clear vision then forces him to relax his accommodation as much as possible. If, on the other hand, the vision of the patient is more highly impaired by the interposition of convex glasses, he is myopic and requires spectacles with concave lenses. In this case, the lenses prescribed for him, should be the weakest with which he is still able to see clearly, because this forces him to bring his ciliary mechanism into physiological play. It is evident that this test should also be made separately for each eye. Instead of the test letters, ordinary print held at the proper reading distance, may be used.

The Ophthalmoscopic Method.—The eye is a camera obscura, and its interior is not open to direct inspection, because the choroid and iris are pigmented and practically impermeable to light. Even in the albino, nothing more than a slight "reflex" sensation of pink is obtained. The fundus of the eye also remains absolutely invisible if we look through the pupillar orifice, because we must then assume a position directly in front of the head of the observed person. Obviously, the rays of light are thereby prevented from entering the vitreous chamber. In some animals, however, the visual axes are more divergent so that the rays can get past the observer's head to illuminate the retina.

Whenever light is reflected into an eye, a large part of it is absorbed by the pigment of the choroid, while a small portion of it is refracted outward into space in the same direction in which it entered. It must be evident that if a luminous point in space L is accurately centered upon the retina in L' , this focal point L' emits divergent rays which are again rendered convergent by the lens to be intersected in L . Consequently, L and L' are conjugate foci. This outward refraction is made impossible if we adjust our eyes to look into the pupillar orifice of the patient, because we thereby cut off the supply of light rays and render the retina non-luminous. In 1851 Helmholtz conceived the idea of illuminating the eye from a lateral source of light by means of three mirrors placed at an angle of 56° to the line of light. This instrument which he called the ophthalmoscope (Fig. 463), has been modified repeatedly, but the principle involved in its construction has remained the same. In its modern form it consists of a concave silvered mirror by means of which light is reflected into the patient's eye from a gas-

lamp adjusted laterally to his head. Since the constriction of the iris would seriously interfere with this examination, this mechanism is temporarily paralyzed by means of atropin. Some mirrors are equipped with a small electric lamp (Dennett's or Marple's modification) which enables us to examine the eyes of bedridden patients and also obviates in a measure the use of atropine.¹ In the center of the

FIG. 463.—LORING'S OPHTHALMOSCOPE, WITH TILTING MIRROR, COMPLETE DISC OF LENSES FROM -1 TO -8 AND 0 TO $+7$, AND SUPPLEMENTAL QUADRANT CONTAINING ± 0.5 AND ± 16 D. THIS AFFORDS 66 GLASSES OR COMBINATIONS FROM $+23$ TO -24 D.

reflecting mirror is a small opening which is adjusted directly in front of the pupil of the observer's eye. We may then follow either the direct or the indirect method of ophthalmoscopic examination.

The Direct Method.—If the eye of the observer is not emmetropic, it should first be made so by spectacles (Fig. 464). The mirror (*m*) is held close to the observed eye, so that the rays reflected from it are able to spread out widely upon the opposing retina (*A'B'*). The area of the retina so illuminated remits rays (*L*) which traverse the dioptric media of this eye and are sent outward into space. Now, it is evident that the emmetropic eye remits these rays parallel to the visual

¹ Large ophthalmoscopes have been constructed by Gullstrand and others. The first gives a magnification of 5 to 50 times in monocular and 20 times in binocular vision. Hertzell illuminates the eye by means of an 80 candle power electric lamp placed in the patient's mouth (ophthalmodiaphanoscopy).

axis, while the myopic and hypermetropic eyes refract them outward in an oblique direction. Assuming then that the observed person is emmetropic and is accommodating for a far object, the parallel rays emitted by his retina must traverse the central orifice in the mirror and be brought to a precise focus upon the retina of the observer (L^1). The latter thus obtains an erect magnified image of the retina of the observed person. A clear image, however, can only be obtained if both eyes are emmetropic and are accommodated for the distance. Some difficulty may be experienced at first in relaxing the accommodation, but this may be overcome if one imagines himself gazing at an object placed far behind the eye of the patient. A complete relaxation of the eye of the observed person is usually secured by the administration of atropine, which alkaloid temporarily paralyzes the ciliary mechanism. It also dilates the pupil, thereby preventing any interference on the part of the iris with the reflection and refraction of the light.

If the observed eye is myopic,¹ the rays of light emitted by the illuminated area of its retina, are refracted into space as a convergent beam and cannot, therefore, be focalized by the emmetropic and relaxed eye of the observer (Fig. 465). In

FIG. 464.—DIRECT OPHTHALMOSCOPY.

Diagram to illustrate the remittance of the rays of light by an emmetropic eye. O , observer's eye; M , mirror; P , patient's eye; F , the rays FA and FB , illuminate the retina of P by a diffusion circle A^1B^1 ; L , the rays emitted by this luminous point are brought to a precise focus in L^1 of the observer's retina.

order to bring these rays to a precise focus, they must first be rendered less convergent by the interposition of a biconcave lens of sufficient diverging power to overcome their excessive convergence. If the observed eye is hypermetropic (Fig. 466), the rays emitted by its illuminated retina, are divergent and cannot, therefore, enter the pupil of the observer. They may be made to do so, however, by placing a biconvex lens in front of the orifice in the reflecting mirror. The strength of the latter should be such that the formerly divergent rays now intersect in the retina of the relaxed emmetropic eye of the observer.

This method not only allows us to detect errors of refraction, but also to determine the strength of the lens which must be used by the patient in order to render him emmetropic. Clearly, the strength and sign of the lens needed by him to correct his defect, is indicated by the lens which the observer must employ in order to obtain a clear image of his retina. For reasons stated previously, the weakest concave lens should be prescribed for myopia and the strongest convex lens for

¹ If the observer moves his head and ophthalmoscope from side to side, the retinal vessels will appear to move in the same direction in the hypermetropic and in the opposite direction in the myopic eye.

hypermetropia.¹ Astigmatism may also be detected and corrected in this way. In order to form an idea regarding the meridians in which the refraction is defective, we only need to observe the retinal blood-vessels along the horizontal and

FIG. 465.—DIRECT OPHTHALMOSCOPY.

Diagram to illustrate the remittance of the rays of light by the myopic eye. *O*, observer's eye; *M*, mirror; *P*, patient's eye; *F*, the rays *FA* and *FB* illuminate the retina of *P* by a diffusion circle *A¹B¹*; *L*, the rays emitted by this luminous point leave the eye of *P* convergently and must therefore be rendered divergent by the interposition of a concave lens before they can be focalized in *L¹* by the eye of the observer.

vertical planes of the optic disc (Fig. 438). The latter appears as a nearly round or slightly oval area varying in color from grayish pink to a more decided red. Its center is occupied by a light patch marking more exactly the entrance of the retinal blood-vessels. The circumference of the optic papilla appears as a dark,

FIG. 466.—DIRECT OPHTHALMOSCOPY.

Diagram to illustrate the remittance of the rays of light by the hypermetropic eye. *O*, observer's eye; *M*, mirror; *P*, patient's eye; *F*, the rays *FA* and *FB* illuminate the retina of *P* by a diffusion circle *A¹B¹*; *L*, the rays emitted by this luminous point leave the eye of *P* divergently and must therefore be rendered convergent by the interposition of a convex lens before they can be focalized in *L¹* of the eye of the observer.

usually incomplete ring representing the border of the choroid coat. Within this lies a faint white line, indicative of the brim of the sclerotic coat.

¹ If the observer is ametropic and does not employ the necessary glasses during this examination, he must of course make this additional correction.

The Indirect Method.—As the name indicates, indirect ophthalmoscopy consists in the formation of a retinal image in space in front of the observer's eye, the principle involved being similar to that of the compound microscope (Fig. 467). The reflecting mirror is held at about an arm's length from the observed eye (30 cm.). A convex lens of about 20 diopters is then placed close to the latter. Obviously, the purpose of this lens is to gather the rays emerging from the observed eye and to bring them to a focus between it and the observer's eye. This real inverted image in space is regarded by the observer through a lens of about 5 diopters inserted in the orifice of the ophthalmoscope. To see this image clearly, the emmetropic observer must move nearer to or farther away from the patient's eye until his distance equals the focal distance of this lens, viz.: 20 cm. Errors in refraction may be detected by moving the objective lens of 20 diopters farther away from the eye, the image then becoming larger in myopia and smaller in hypermetropia. The observer then interposes different concave (−) and convex (+) lenses until the image becomes perfectly clear.

FIG. 467.—INDIRECT OPHTHALMOSCOPY.

Diagram to illustrate the remittance of the rays of light by an emmetropic eye. *O*, observer's eye; *M*, mirror; *P*, patient's eye; *F*, the rays *FA* and *FB* illuminate the retina of *P* by a diffusion circle *A¹B¹* (inverted in this case) *L*, the rays emitted by these luminous points are converted into a real inverted image in the air at *J*. The latter is then focused upon the observer's retina.

Skiascopy or the Shadow Test (Retinoscopy).—This method consists in determining the direction of the movement of the light in the pupillar orifice when it is made to move back and forth by rotating the reflecting mirror around the long axis of the handle supporting it. It is a matter of common observation that a beam of light reflected against a wall, moves with the reflecting mirror. A similar phenomenon occurs in the human eye if the retina is illuminated so that it can emit light. Thus, if a beam of light is thrown into the eye, the pupil is completely illuminated. If the mirror is now rotated around its long axis, the pupil is darkened on one side and this shadow moves either in the same or in the opposite direction to the rotation according to the position of the observer's eye in the line of vision of the observed eye (Fig. 468). If situated exactly at its far point, the pupil remains either dark or is fully illuminated and does not exhibit a distinct moving shadow. This point indicates the position of the so-called *point of reversal* (*A*). Retinoscopy, therefore, is a method by means of which the distance of this point may be accurately determined. Be-

yond this point (*B*) an inverted image will be obtained, and the light in the pupil will appear to move against the rotation of the mirror, whereas inside *A* the image (*C*) is erect, and the light seems to move with the rotation.

In myopia, the point of reversal lies close to the eye. Consequently, if the observer finds that, on throwing light into the eye, the light in the pupil is against the rotation, he must be beyond the point of reversal. He should then approach the observed eye slowly

FIG. 468.—DIAGRAM TO ILLUSTRATE THE LOCATION OF THE POINT OF REVERSAL AS OBTAINED BY THE SHADOW TEST.

until he finds this movement to be with the rotation. These observations should be repeated until this point has been accurately localized. The distance between this point and the eye should then be measured with the ruler, because it represents the focal distance of the lens necessary to correct the myopia. Thus, if it is possible to obtain an erect movement at a point 55 cm. from the eye and a reversed movement at 80 cm., the exact point of reversal will be at 67 cm. The myopia equals in this case 1.50 D.

FIG. 469.—DIAGRAM TO ILLUSTRATE THE LOCATION OF THE POINT OF REVERSAL AS OBTAINED BY THE SHADOW TEST IN THE HYPERMETROPIC EYE.

In hypermetropia the rays are emitted divergently and hence, a point of reversal cannot be present. The observer then finds that the movement of the light remains with the rotation, no matter how far he withdraws from the eye. A convex lens should now be interposed to form a point of reversal at a convenient distance from it, thereby rendering it artificially myopic (Fig. 469). This point of reversal having been ascertained with the ruler, the degree of myopia represented by it is then subtracted from the total strength of this lens. The remainder

corresponds to the power which is required to correct the divergence of the rays, *i.e.*, the hypermetropia. Thus, if a lens of 5D is employed and the movement of the light remains with the rotation of the mirror until a little within a distance of 1 m. but is reversed at a distance of a little more than 1 m., the point of reversal is at 1 m. Consequently, 1D of the strength of this lens is required to converge the rays, while 4D of the total 5D have been made use of in overcoming the divergency of the rays upon their projection from the observed eye. In this case, the hypermetropia equals 4D.

In astigmatism the same method may be followed, but these tests must then be repeated for different meridians, *i.e.*, the point of reversal must be ascertained separately for the horizontal, vertical and oblique planes.

CHAPTER LXXIV

BINOCULAR VISION

The Movements of the Eyeballs.—The organ of vision consists of the globe of the eye, measuring nearly an inch from side to side, slightly less than an inch from above downward and somewhat more than an inch from before backward. Its volume equals 6.5 cm. and its weight nearly 7 grams. Connected with it externally are different muscles, nerves and blood-vessels. It is supported by a quantity of fat and connective tissue, the latter forming a lymphatic space known as the capsule of Tenon. Within this capsule the eyeball is made to move by the contraction of a set of muscles, designated as the ocular muscles. These are the four recti and two oblique muscles. The former, which are known respectively as the superior, inferior, external and internal, take their origin from a tendinous ring investing the optic foramen and sphenoidal fissure. From here they pass forward along the walls of the orbital cavity and finally perforate the aforesaid lymphatic space to gain access to the equatorial region of the eyeball. Closely investing the latter, they finally terminate in their respective positions about 7 mm. posterior to the margin of the cornea. The superior oblique muscle arises from a small tendon upon the inner margin of the optic foramen and, passing forward to the inner angle of the orbit, terminates in a rounded tendon which plays in a pulley of fibro-cartilaginous tissue suspended from the depression in the internal angular process of the frontal bone. From here this tendon is reflected backward, outward and downward upon the outer part of the eyeball about midway between its cornea and the entrance of the optic nerve. The inferior oblique muscle arises from a depression in the orbital plate of the superior maxillary bone, external

to the lacrimal groove. From here it passes outward, upward and backward, and finally ends in a tendinous expansion which is inserted in the sclera upon the outer part of the eyeball, near to but somewhat behind the tendon of the superior oblique.

The movements of the eyeball are similar to those of the head of a long bone within its socket, an unrestricted motion being made impossible by several resistances, such as the insertion of the different muscles, the capsular aponeurosis and the entrance of the optic nerve. The recti muscles act antagonistic to one another, the range of con-

FIG. 470.—DIAGRAM SHOWING THE LINES OF INSERTION OF THE OCULAR MUSCLES INTO THE SCLEROTIC. (Merkel and Kallins.)

I, Globe from above; II, from the nasal side; III, from below; IV, from the temporal side. *s*, rectus superior; *i*, rectus inferior; *m*, rectus internus (*s. mesialis*); *e*, rectus externus (*s. lateralis*); *os*, obliquus superior; *oi*, obliquus inferior.

traction of one being restricted by the extension of the opposite one. Their action, however, is unable to pull the eyeball backward owing to the antagonistic action of the smooth musculature of Tenon's capsule. In some animals, such as the reptilia and amphibia and several mammals, a movement of this kind is effected by a special muscle known as the retractor bulbi.

The globe of the eye does not alter its position in rotating, but is merely turned around its axes. Thus, if it stated that the eye is moved upward, reference is had merely to the relative position of its anterior and posterior poles. While the cornea moves upward, the back of the eyeball moves downward, and *vice versa*. Although the axes around which the eye may be rotated are many, it is customary to recognize

three principal ones, namely, two horizontal and one vertical. All three traverse the center of rotation at right angles to one another, allowing the following movements of the eye to be executed: (a) outward or inward around its vertical axis, giving rise to its average abduction or adduction, (b) upward or downward around its transverse horizontal axis, and (c) around its sagittal axis connecting its anterior and posterior poles. The only movements carried on by the contraction of one muscle, or rather, by the reciprocal action of a single pair of muscles, are abduction and adduction. The former is accomplished by the external rectus and the latter, by the internal rectus. Movements upward or downward necessitate the contraction of at least two muscles, the former being mediated by the superior rectus and inferior oblique, and the latter by the inferior rectus and superior oblique. When acting singly, the superior rectus draws the cornea upward and inward. This action is combined with that of the inferior oblique which draws it upward and outward, but would also, theoretically considered, rotate the eyeball outward around its sagittal axis. Quite similarly, the inferior rectus, when acting alone, pulls the cornea downward, but also adducts it and should rotate it outward. The superior oblique, on the other hand, deviates the cornea downward and slightly outward, but should also turn it inward.

It should be emphasized, however, that a rotation of the eyeball around its antero-posterior axis does not take place under ordinary conditions, although the course of these four muscles might warrant us to assume such an action. This point may be proved by first gazing at the vertical filaments of an electric lamp and then resting the eyes upon a uniform gray surface. The after-image of these luminous lines which will then be formed, shows them in their original vertical position no matter whether the eye be turned upward, downward or in an oblique direction. Naturally, if the eye were actually turned around its antero-posterior axis, the after-image of these filaments should really assume a slanting position. Movements of the eyeballs around oblique axes require the coöperation of three muscles, viz.:

(a) Upward and outward; superior rectus, inferior oblique and external rectus.

FIG. 471.—DIAGRAM TO SHOW POINTS OF ATTACHMENT AND LINES OF ACTION OF EXTRINSIC OCULAR MUSCLES. (Landois.)

(b) Upward and inward; superior rectus, inferior oblique and internal rectus.

(c) Downward and outward; inferior rectus, superior oblique and external rectus.

(d) Downward and inward; inferior rectus, superior oblique and internal rectus.

Binocular Vision.—In man the movements of the eyes are bilateral, each eye being moved around its center of rotation, situated 13.5 mm. behind the cornea or 1.3 mm. behind the middle of the eyeball. When the head is held erect and the eyes are directed to a point at the horizon, their visual axes are parallel to one another. This constitutes the primary position. When the eyes are moved directly upward, downward, outward or inward, they occupy secondary positions and when turned in oblique directions, tertiary positions. The movements of the two eyes are correlated by a central mass of gray matter,¹ the

FIG. 472.—DIAGRAMS TO SHOW HOMONYMOUS AND HETERONYMOUS DIPLOPIA.

In I the eyes are focused on A; the images of B fall on non-corresponding points,—that is, on different sides of the foveæ, and are seen double, being projected to the plane of A, giving heteronymous diplopia. In II the eyes are focused on the nearer point, A, and the farther point, B, forms images on non-corresponding points and is seen double—homonymous diplopia—the images being projected to the focal plane A.

anatomical basis for the bilateral character of their innervation being furnished by the fact that each oculomotor nerve is composed of fibers derived from both nuclei and that the latter are intimately connected with one another by commissural fibers. Two chief types of movements may be recognized, namely:

(a) Movements during which the visual axes of the eyes are kept practically parallel to one another, no matter whether they are deviated along the vertical plane of the visual field or laterally outward. Naturally, this parallelism can only be maintained if the object remains at some distance from the eyes.

(b) Movements during which the visual axes are converged in order to be able to observe objects near the eyes. This convergence results invariably during near vision and is therefore accompanied by the contraction of the ciliary muscle.

Converging movements of the eyeballs directed at objects situated laterally from us, may also be executed, but since these require an

¹ Hering's Law of Uniform Innervation, Hermann's Handb. der Physiol., 1879, III, 343.

extra effort, they are usually supplemented by movements of the head as a whole. This furnishes a much simpler means of bringing the object into direct opposition with the yellow spots. Furthermore, it will be noted that the convergence of the eyes necessitates a symmetrical innervation of the internal recti muscles, while a symmetrical innervation of the external recti is quite superfluous, because we do not diverge the visual axes during normal vision. In fact, a movement of this kind would give rise to the condition of diplopia or double vision, for the obvious reason that the rays of light would then be made to fall upon areas of the retina which are not psychically correlated. A condition of diplopia, however, may be established without much difficulty by exerting a gentle pressure upon one eyeball, so that it is momentarily forced out of its normal position. Since the retinae of the two eyes are then activated in dissimilar areas, a double impression in consciousness is the natural consequence.

Diplopia is a common symptom of certain disorders of the nervous system, leading to disturbances in the coördinated action of the different orbital muscles. It is true, however, that slight divergencies are generally compensated for volitionally by simply causing the weaker muscle to contract more forcibly than it would otherwise, but naturally, a point will eventually be reached when these extra efforts cease to produce the desired effect. A condition characterized by a partial loss of balance of the eye muscles, is designated as heterophoria, and one characterized by a more complete loss, as strabismus or squint. In the latter case, the person is quite unable to direct the visual axes jointly upon the object, but double vision need not result even then, unless the strabismus is very pronounced or has arisen very suddenly in consequence of some injury. Most generally, the patient learns by experience to base his visual associations upon the impressions derived from the more normal eye, and ignores or suppresses the image from the non-corresponding area of the opposite retina. Heterophoria, as well as strabismus, may be mitigated or remedied altogether by the use of prisms.

This discussion shows that single vision with the two eyes is due to a fusion of the visual impressions in consciousness, and is largely the result of experience. Thus, we speak of "corresponding points" upon the retina, although it must be evident that a certain cone in one retina cannot act in unison with a cone occupying the same position in the opposite retina. The aforesaid term, therefore, is not indicative of a histological identity, but of an identity in function. Consequently, while certain areas in the two retinae may be correlated functionally, they are not symmetrically placed. This fusion of the visual impressions in consciousness may be illustrated in the following ways:

(a) If the right eye is made to receive a certain impression of red and the left eye, an identical impression of blue, the result is either a fusion of the two colored fields (purple) or a struggle of the two fields for supremacy. In the latter case, a sensation of red alternates with a sensation of blue.

(b) If the right eye is made to receive a figure composed of horizontal lines and the left eye one composed of vertical lines, the result is a struggle between these impressions. Sometimes the former and sometimes the latter gains the upper hand.

The sum total of the corresponding points in the binocular field of vision producing a single impression, forms the so-called *horopter*.¹ It differs with every new position of the eyes and may be a straight or a curved line, a plane or a curved surface.

Visual Judgments.—It has been pointed out repeatedly that our visual impressions in consciousness are the result of experience. Like other sense-organs, our eyes are the mere recipients of stimuli which are moulded into concepts within the cortical realm of vision and these concepts are acquired gradually by constant repetition. 'To begin with, the infant receives these stimuli without being able to interpret them, because its association areas are as yet incompletely developed. In the course of a few months, however, it begins to form simple concepts. It follows the course of a moving light with its eyes and also responds in other ways to stimuli of this kind. A few months later it has learned to associate objects in space in their proper relations, irrespective of the fact that the images upon the rods and cones are inverted.

The adult being, therefore, is guided by the associations thus gradually acquired and does not concern himself with the manner in which the images are formed in the sense-organ, *i.e.*, the fact that the objects in space are presented to him inverted he has overcome by experience and proper psychic interpretation. The visual concepts thus formed are gradually brought into relation with concepts of a different nature, so that, for example, the visual concept of a certain object is subsequently correlated with its taste and odor or with the sound which it may produce. A similar expansion of our concepts enables us to form judgments not only regarding the *general outline* of objects but also regarding their *depth* or *solidity*. Although the most perfect results are obtained by binocular vision, one eye is quite sufficient to obtain correct relationships in space, and to rate objects in accordance with their height, breadth and depth. Obviously, the judgment of the size of an object is chiefly dependent upon the size of its image upon the retina and hence, upon the angles which its luminous rays form with the visual angles of the eyes. This requires accommodation by the ciliary mechanism as well as variations in the position of the visual axes of the eyes. Since an object at a distance of 5 m. emits a large number of parallel rays, practically no accommodation is required. Beyond this point, we must rely chiefly upon the visual angle, while within this distance, this factor is augmented by the degree of contraction of the ciliary muscle as well as by that of the orbital muscles used in converging the visual axes. Lastly, our associations are based upon certain outside factors, for example, the character

¹ Johannes Müller, Beitr. zur vergl. Physiol. der Sinnesorgane, 1826.

of the air. Inasmuch as the latter is not entirely transparent, distant objects cannot be seen so clearly as near objects. In many cases, this obscuration of the luminous rays of an object frequently prompts us to form an erroneous judgment. Thus, an object dimmed by a mist "looms large," because we associate indistinct vision with distance and hence, the sudden relatively large visual image produced by this near object, leads us to overestimate its actual size. Concurrently, the size of an object seen in a clear atmosphere, is

FIG. 473.—RIGHT- AND LEFT-EYED IMAGES OF TRUNCATED PYRAMID. MAY BE COMBINED TO PRODUCE SOLID IMAGE BY RELAXING THE ACCOMMODATION—THAT IS, GAZING TO A DISTANCE THROUGH THE BOOK.

generally under-valued for the reason that distinct vision is associated with near objects.

The judgments regarding the depth or solidity of objects are formed in a similar way, *i.e.*, they are based upon several factors, namely:

(a) The difference, in the images formed in the two eyes. Since the eyes are separated from one another by a certain distance, the right eye sees more of its right side and the left eye, more of its left side. This difference in the projection

FIG. 474.—STEREOSCOPIC PICTURE OF AN OCTAHEDRAL CRYSTAL. MAY BE COMBINED STEREOSCOPICALLY BY RELAXING THE ACCOMMODATION BY THE METHOD OF HETERONYMOUS DIPLOPIA. HOLD THE OBJECT AT A DISTANCE OF A FOOT OR MORE AND GAZE BEYOND.

leads to a corresponding difference in the associations. It becomes more pronounced, the nearer the object.

(b) Mathematical perspective. Objects appear in relief and we have learned to interpret perspective correctly.

(c) Lights and shadows aid our judgment according to their distribution through the visual field.

(d) The muscle-sense plays a part in accommodation as well as in the convergence of the visual axes.

(e) Condition of the atmosphere. More distant objects are not so clear as near objects.

The Stereoscope.—The purpose of this instrument is to fuse non-corresponding images so that they may give rise to a single visual concept possessing solidity. Wheatstone¹ accomplished this end by means of mirrors placed at certain angles to one another, and Brewster² by means of two prisms. It has been stated above that the images of a solid object in binocular vision, are somewhat different in the two eyes, but since they are formed upon corresponding points of the retinae, they produce a perfectly harmonious relief.

The stereoscope serves to give solidity to pictures of objects which would otherwise present only two dimensions, namely those of height

FIG. 475.—DIAGRAM TO ILLUSTRATE THE PRINCIPLE OF THE BREWSTER STEREOSCOPE.

P and P' , the prisms. a, b , and a', b' , the left- and right-eyed pictures, respectively, b, β , being a point in the foreground and a, a' , a point in the background. The eyes are converged and focused separately for each point as in viewing naturally an object of three dimensions. (*Landois.*)

and breadth. This fusion of two pictures is effected by permitting each eye to regard its own field through a curved prism composed of two half lenses with convex surfaces, the inner margins of which are directed inward. A vertical screen is adjusted between the two lenses in such a way that the sight of the left eye is entirely cut off from that of the right eye (Fig. 475). While the prisms themselves tend to magnify the pictures, stereoscopic views are usually taken with the help of two lenses which are separated by a distance somewhat greater than the interocular. Consequently, the solidity is in reality somewhat exaggerated. It has been pointed out above that two identical pictures cannot give a sensation of relief, because only the psychic comparison of two slightly dissimilar images can lead to a perception of solidity. In other words, we have learned by experience that only those objects can give rise to

this impression which possess solidity. Upon this basis rests the psychic interpretation of stereoscopic pictures.

Optical Illusions.—It appears, therefore, that seeing is essentially a process of reasoning in accordance with past experience. This point is clearly proved by the visual sensations of blind persons whose sight has been restored in later years by the sudden relief of the condition causing the blindness. Although these persons have gradually formed an idea regarding the shape and size of objects by means of the muscle-sense, they are then quite unable to tell "which is which," and several days of repeated comparison are required

¹ Phil. transactions, 1838.

² Edinburgh Phil. Transactions, 1843; also: Rollman, Poggend. Annalen, 1853.

before they are able to correlate their visual concepts with those previously established with the help of the muscle-sense. Thus, one person could not tell which was the dog and which the cat, concepts formed solely by the muscle-sense, until he had again felt of the cat's tail and general contours of its body. In all these cases, the persons made

FIG. 476.—TO ILLUSTRATE THE ILLUSION OF SUBDIVIDED SPACE.

protective movements, because they felt as if the objects were actually touching their eyes.

While our visual judgment is something quite definite, we are very prone to form wrong concepts whenever we are subjected to unusual

FIG. 477.—TO ILLUSTRATE THE OVER-ESTIMATION OF VERTICAL LINES.

conditions, such as may be established by changing the position of our body as a whole or by altering the configuration of the object. Thus, a space subdivided by intermediate lines seems larger than one not so interrupted. Evidently, it requires a somewhat greater muscular

effort to focalize these lines in succession than if the eyes can sweep straight across the open field. Quite similarly, if two equally large squares are subdivided by an equal number of horizontal or vertical lines, the one subdivided horizontally will appear to be larger from below upward and the other from side to side (Fig. 476). If we adjust two lines of equal length at right angles to one another, the vertical

FIG. 478.—ZÖLLNER'S LINES.

one will seem to be the longer of the two (Fig. 477). This deception has been explained by assuming that the contraction of the internal or external oblique muscle, required to visualize the horizontal line, is effected with a slighter expenditure of energy than that of the oblique muscles, required to trace the vertical line. In the latter case, the tendency of the superior rectus to divert the eye inward, must be

FIG. 479.—MÜLLER-LYER FIGURES TO SHOW ILLUSION IN SPACE PERCEPTION. THE LINES *A* AND *B* ARE OF THE SAME LENGTH.

counteracted by the contraction of the inferior oblique which turns the eye outward.

A very striking illusion may also be produced by placing convergent and divergent oblique lines upon two parallel lines of the same length. In the first case, the latter will appear to come together, and in the second case, to separate more widely. A similar effect may be ob-

tained with the aid of the so-called Zöllner's lines, represented in Figure 478. This illusion may be explained upon the basis that we tend to overvalue the size of acute angles. Figure 479 shows two horizontal lines of the same length which, however, are made to appear distinctly unequal by oblique lines affixed to their end-points. Illusions of movement are now extensively employed in cinematographic pictures. A series of instantaneous photographs having been taken of a moving object while assuming its successive positions, these pictures may in turn be thrown upon the retina in rapid succession reproducing the original movement.

CHAPTER LXXV

COLOR VISION

Qualities of Light.—The ethereal vibrations which are capable of affecting our retinae, have different vibratory qualities. White light, such as is emitted by the sun, is made up of rays of different wave lengths or rapidity of vibration. Consequently, if a beam of this light is made to impinge upon a plane medium of greater density, it is split into its component rays. Those possessing the more rapid vibratory rate, are retarded or refracted more sharply than those characterized by a slow vibration. If the aforesaid medium is arranged in the form of a prism, this "dispersion" or spreading of the different rays will be even more apparent. We then obtain the so-called prismatic or solar spectrum (Newton 1657), consisting of seven primary colors, namely red, orange, yellow, green, blue, indigo and violet. These colors, however, form a continuous series and gradually shade into one another. Those which stimulate our retinae vary in their vibratory rate between 392,000,000,000,000 and 757,000,000,000,000 in a second. In round numbers, therefore, it may be said that we are subject to rays, the wave lengths of which vary between 400μ to 800μ .¹ Under ordinary conditions, however, we do not recognize the existence of these rays, because our eyes do not possess the means of resolving white light into its constituents. Consequently, this analysis can only be made outside of this receptor, and only when the retina is subjected to these rays separately, are we in a position to recognize colors. In this regard, our eyes differ very materially from the ear, because the latter is equipped with a mechanism for analyzing sound, *i. e.*, for resolving the compound waves into their simple components. It should also be remembered that the spectrum contains other rays beyond its red and violet ends, and while the latter do not activate the retinae, they may be made to do so by accessory means.

¹ 1μ equals $\frac{1}{1,000,000}$ mm.

Beyond the red we have rays of greater wave length, the so-called heat-rays, and beyond the violet, rays of smaller wave-length, the so-called chemical rays. The ultra-violet variety, however, may be raised above the threshold of stimulation by rendering them fluorescent. This is true of the Becquerel (radium) and Röntgen rays, the latter causing a fluorescence of the retina.¹

It will be seen, therefore, that the sensations of color are due to impacts upon the retina of ether waves of definite length, whether they be derived from a homogeneous beam or from a mixture of simple lights. Besides the mere *color* which is dependent upon the rate of vibration, these sensations are also modified by the intensity or energy of the vibrations as well as by the saturation of the primary color. The intensity of the stimulation gives rise to *luminosity* or *brightness*. Thus, it will be found that the extreme red and violet ends of the spectrum are less luminous than the yellow. Furthermore, while we are able to tell which of two red or green colors is the brighter and are even able to match them by increasing the intensity of the beam of light, we fail absolutely when attempting to arrange different colors in strict accordance with their brightness. These tests, however, may be greatly varied by changing the illumination. This is shown by the fact that a colored object appears colorless in low intensities of light, and that the brightness of the spectrum is then shifted from the yellow to the green (Purkinje's phenomenon). The *saturation* of a color is dependent upon its admixture with white light. Thus, a perfectly saturated color is one entirely free from ordinary white light, and a thoroughly colored object, one which reflects specific color rays and no white rays. Physically, it is not difficult to establish this condition, because all we need to do is to restrict the beam of light to specific spectral rays. Physiologically, on the other hand, color sensations are generally not pure, because even monochromatic light appears to give rise to sensations of white which are thus made to intermingle with the particular color sensation. In other words, while the physical saturation of a color may be complete, the physiological saturation is generally incomplete.

Color Fusion.—In the same way as white light may be divided into its components, so may the different spectral colors be reunited into white light. This can be done very easily by placing suitable lenses in the path of the colored rays emerging from a prism. It should also be noted that white light may be produced by combining only two, three, four, five, or six of the original seven spectral colors. Any two colors which give rise to a sensation of white are known as "*complementary colors*."

A device most commonly employed to stimulate the retina simultaneously with two or more colors is the color-wheel of Maxwell. It consists of a rotating axis to which may be attached discs of colored

¹ Birch-Hirschfeld, Archiv für Ophthalm., lviii, 1904, 469.

pasteboard. The latter are slit radially from periphery to center so that they may be lapped over each other to expose a larger or smaller segment of each. Another method is to superimpose different sections of the spectrum upon a screen by means of a system of lenses or mirrors. In either case, this physiological mixing of colors cannot be compared with that employed by the painter. Thus, a blue and yellow pigment when mixed, give rise to the sensation of green and not of white, because these two colors combined absorb all the rays excepting the green, the latter only being reflected into the eye. When used alone, the former appears blue, because it allows only the blue and some of the green rays to be reflected, while the latter appears yellow because it absorbs all the rays excepting the yellow. Consequently, when we mix these colors we obtain a subtraction, the blue pigment

FIG. 480.—ROTHE'S ROTATORY APPARATUS FOR COLOR DISCS. IT IS SO ARRANGED AS TO GIVE VARIOUS RATES OF ROTATION BY COMBINING THE MOTIONS OF 1, 2, AND 3.

absorbing the red rays which the yellow pigment lets pass, while the yellow pigment absorbs the blue rays which the blue allows to pass. Thus, only the green rays are left over.

The colors which may be arranged in a series of pairs to give white are the following:

	Wave-lengths.
Red and greenish blue.....	656-492
Orange and blue.....	608-490
Bright yellow and blue.....	574-482
Yellow and indigo.....	567-465
Greenish yellow and violet.....	564-433

The fusion of a pair of colors lying closer together than their complementary colors, yields an intermediate color which becomes more completely saturated or free from white, the nearer they are to one another. Thus, the union of red and yellow gives rise to orange, but the latter is less saturated than the corresponding spectral color. In the former instances, for example, rays of $656 \mu\mu$ and $564 \mu\mu$ are

mixed, while the spectral orange possesses a wave length of 608 $\mu\mu$. Colors which are more widely separated than the complementary colors, produce a sensation of purple which is not a spectral color at all but may be obtained by combining red with violet, the two spectral extremes. If one or the other of a pair of complementary colors is added in excess, the resultant sensation is a color similar to the one present in excess with more white mixed in with it. Supposing that we employ orange and blue, with the blue present in greater amount than is necessary to produce white, the result is an unsaturated blue, *i.e.*, pale blue.

Visual After-effects.—The fusion of the colors described in the preceding paragraphs, depends upon the persistence of the individual stimulations, a second color being thrown upon the retina before the first sensation has had sufficient time to disappear. This is really true of all visual impressions, because they invariably last longer than the stimulus. Everything else remaining equal, these after-images depend in a large measure upon the intensity of the primary stimulus, *i.e.*, upon its strength and duration. Thus, an electric spark generally leaves a very decided impression in consciousness, because it is intense although of very brief duration. Quite similarly, if one looks at the light of a candle, and then closes his eyes, this image persists for some time thereafter in its natural colors. It then fades away, meanwhile undergoing certain changes from greenish blue to indigo, violet, rose and pale orange. But this phenomenon is not restricted to mere white-black impressions, but also to specific colors. In any case, we designate them as *positive after-images*, because they do not change their original character. *Negative after-images*, on the other hand, do not retain their character, but assume colors complementary to those of the object producing them. White becomes black, red a bluish green, yellow an indigo blue, and so on. These images are obtained more frequently than those of the positive kind and may be produced in the following way. If we gaze intently for a few moments at a red disc upon a white surface and then at a uniform white background, an after-image of this disc is obtained which, however, appears green, while the background assumes a reddish shade. This phenomenon is usually explained upon the basis of fatigue of the retina toward this particular color, although it is difficult to reconcile this hypothesis with all the facts. Nevertheless, it is easy to understand that the after-image must appear in the complementary color, because the retinal component producing the sensation, say of red, has been considerably reduced by the exposure, while its greenish-blue element is still present in normal amounts and is, therefore, still able to produce its characteristic effect.

Contrast.—If we place a small white disc upon a larger black field, the former appears whiter than it would if not contrasted in this way. Quite similarly, a small black dot adjusted upon a white general field appears much darker in color than one resting upon a background of

another quality, and a piece of red paper held against a red background, does not appear nearly so saturated as one contrasted, say, against white. A similar contrast may be obtained by rotating a white disc containing a certain amount of black, as illustrated in Fig. 481. On rotation this disc ought to yield uniform circles of gray, their brightness being least in the center. Instead, each circle presents a darker outer and lighter inner margin, because the former borders on a zone darker than itself, while the latter borders upon a zone lighter than itself.

These phenomena of contrast may also be extended to colors. Thus, if a piece of gray paper is placed upon a larger green sheet, the former appears pink or rose-red. The intensity of the latter color may be increased by covering the whole with a sheet of tissue-paper. It may also be illustrated by the approximation of colored shadows.

FIG. 481.—A, BLACK AND WHITE DISC FOR EXPERIMENT ON CONTRAST; B, SHOWING THE RESULT WHEN THE DISC A IS SET INTO RAPID ROTATION. (Rood.)

This can be done by placing an object of suitable size and shape upon a white background and illuminating it from one side with day-light and from the other with gas-light. Two shadows result which are sharply contrasted against one another. The one thrown by the gas-light appears yellow, while the one produced by the day-light exhibits a bluish tint, for the reason that it is contrasted against the general yellowish illumination.

The hypothesis of Helmholtz which refers contrast to an erroneous judgment, has been severely criticized by Hering who holds that this phenomenon is due to the opposing influences of two different regions of the retina and the visual association areas corresponding to them. Hering, therefore, ascribes them to the peripheral part of the visual mechanism and removes from them any purely psychic character. Evidently, he imagines them to be opposing processes of assimilation and dissimilation, similar to those occurring during color vision. This implies that while a dissimilation of a particular substance may be going on in one part of the retina, a neighboring area may show assimilation. McDougall compares these phenomena of contrast to the

inhibitor processes going on in the spinal cord during reciprocal innervation. It has been pointed out by Sherrington that the extensor or stepping reflex may be inhibited by evoking the flexor reflex. In an analogous manner it is supposed here that the excitation of one part of the retina prevents similar processes from developing in neighboring regions or in the neurons innervating them.

The Sensibility of the Retina to Colors.—It will be remembered that the perimeter is used to map out the visual field for ordinary objects. It may also be employed for studying the distribution of the color sense by simply replacing the small white disc by discs of different colored paper. By bringing the latter into the line of vision along the different meridians of the eye, it will be found that the extreme outer zone of the retina is color blind and perceives only

FIG. 482.—PERIMETER CHART INDICATING THE AVERAGE FIELDS OF VISION FOR BLUE, RED, AND GREEN COMPARED WITH WHITE (GRAY). (Howell.)

objects as such. Somewhat nearer the center of the visual field, we perceive first blue, then red, and lastly, green. Consequently, the retina may be divided into three concentric color zones, namely, a peripheral one for black and white, an intermediate one for yellow and blue, and a central one for red and green. It is to be noted, however, that these zones are rarely identical in the retinae of different individuals and may even present marked irregularities in one and the same person. But, many of these variations are referable to differences in the relative saturation of the colors employed for this test.¹ Most

¹ Baird, The color sensibility of the peripheral retina, Publ. Carnegie Institution, No. 29, 1905.

peculiar abridgments of the color field result in consequence of diseases of the retina, and optic nerve or of lesions of the visual association area.

FIG. 483.—PERIMETER CHART SHOWING THE HIGHLY RESTRICTED COLOR FIELDS IN THE LEFT EYE OF A TYPICAL CASE OF SO-CALLED RED-GREEN COLOR BLINDNESS. (Howell.)

Theories of Color Vision.—It has been pointed out above that the rods and cones are somewhat different in their function. From the standpoint of color vision it is now commonly believed that the former

FIG. 484.—DIAGRAM TO ILLUSTRATE THE YOUNG-HELMHOLTZ THEORY OF COLOR VISION. VERTICALS DRAWN AT ANY POINT OF THE SPECTRUM INDICATE THE RELATIVE AMOUNT OF STIMULATION OF THE THREE SUBSTANCES FOR THAT WAVE LENGTH OF THE SPECTRUM. (Helmholtz.)

which alone are present in the zone adjacent to the ora serrata, are concerned with achromatic vision in low intensities of light, while the latter are employed for color vision as well as for achromatic vision in ordinary intensities of light. This conclusion, however, does not

furnish an adequate explanation for this function, but simply leads to certain assumptions which have been embodied in the theories now to be discussed.¹ It must be emphasized, however, that the latter are really mere hypotheses lacking a sound experimental basis. All of them assume the existence in the retina of certain fundamental substances which are instrumental in effecting the primary sensations of color, and the only difference between them really lies in the manner in which these pigments are distributed.

The *Young-Helmholtz theory* which was first advocated by Young but has later on been greatly elaborated by Helmholtz,² assumes the presence of three primary color sensations, designated as red, green and violet (Fig. 484, 1, 2 and 3). These sensations arise in consequence of the activation of three separate photo-chemical

FIG. 485.—DIAGRAM TO ILLUSTRATE THE HERING THEORY OF COLOR VISION.

The curves indicate the relative intensities of stimulation of the three color substances by different parts of the spectrum. Ordinates above the axis, X-X, indicate catabolic changes (dissimilation), those below anabolic changes (assimilation). Curve *a* represents the conditions for the black-white substance. It is stimulated by all the rays of the visible spectrum with maximum intensity in the yellow. Curve *c* represents the red-green substance, the longer wave lengths causing dissimilation (red), the shorter ones assimilation (green). Curve *b* gives the conditions for the yellow-blue substance. (Poster.)

substances which, on being struck by the rays of light, undergo a decomposition and generate nerve impulses peculiar to each of them. The red substance is reduced by the rays of long wave-length, the green substance by rays of medium wave-length, and the violet substance by rays of short wave-length. When these chemical elements are excited in an equal measure, the result is the sensation of white or gray, while no stimulation at all yields black. The other sensations of color are compound in their nature, *i.e.*, they are dependent upon the joint stimulation of all three substances in different proportions. Thus, yellow is the result of an excitation of the red and green elements and blue, the result of an activation of the green and violet substances.

The *Hering theory* of color vision assumes the presence of four primary sensations of color, namely, red, yellow, green and blue. These sensations, however, are supposed to be produced by two groups of photo-chemical substances, namely, red-

¹ Calkins, *Archiv für Physiol.*, 1902, 244.

² *Handb. der physiol. Optik*, Berlin, 1896.

green and yellow-blue. To these is then added a white-black substance, so that we have in reality three pairs of recipient elements. Actual sensations of color are derived from these groups of substances by processes of assimilation and dissimulation, as follows:

	Dissimulation	Assimilation
Red-green.....	red.....	green
Yellow-blue.....	yellow.....	blue
White-black.....	white.....	black

Like all other constituents of our body, these substances are first broken down and then again reformed. They undergo catabolism and anabolism. Thus, if white light falls upon the retina, the white-black pigment is reduced, this process giving rise in consciousness to the sensation of white. As soon as this stimulation ceases, the white-black substance is reformed, setting up in consciousness the sensation of black. But, this recipient is also affected by rays of different wave-lengths so that the sensations of white and black frequently occur together with those of the other colors. The yellow-blue and red-green recipient elements, however, are affected exclusively by rays of their specific wave-lengths.

The *Ladd-Franklin theory* of color vision¹ assumes that the colorless sensations of white, gray and black are produced by the excitation of a photo-chemical substance, designated as gray. While this recipient element is present in the rods as well as in the cones, only the latter contain it in a form to give rise to sensations of different colors. On exposure to light this substance is dissociated, the result being different shades of gray. This is the only reaction possible in the rods, and hence, these elements give rise exclusively to this particular sensation. In the cones, on the other hand, this substance is present in a differentiated form, allowing the development of more complex reactions. The molecules of gray substance here assume a multiple form so that only certain portions of them are dissociated by the light. The molecular substance is divided into two parts, one of which is sensitive to the rays of slow vibration, and the other to those of rapid vibration. The excitation of the first yields yellow and that of the second blue. The yellow recipient is again divided into two parts, one of which receives the longest visible rays (red) and the other the rays giving rise to the spectral green. Thus, the complete dissociation of the red, green and blue recipients produces gray, while the simultaneous dissociation of the red and green evokes the same sensation as the dissociation of the entire yellow recipient.

Since this theory necessitates certain new chemical conceptions pertaining to the differentiation of the molecule, and its complete and partial dissociation, it cannot be regarded as anything more than a provisional explanation until definite experimental proof has been furnished for these contentions. It is true, however, that it accounts for certain facts pertaining to color-blindness in a more accurate manner than the two theories mentioned previously. In addition, it furnishes an explanation for the variations in the visual sensations mediated by the peripheral zone of the retina.

Color-blindness.—The terms of amblyopia and amaurosis are employed to indicate an obscurity and loss of sight. In this category are also placed certain congenital defects of the sense of color which are present in about 3 per cent. of the eyes examined, but are relatively rare in woman. In most cases, both eyes are affected and a hereditary tendency is unmistakable. It also seems that this disorder is more common among the poorly educated classes.²

¹ Psychological Review, 1894, 1896 and 1899.

² Holmgren, Color Blindness in its Relations to Accidents by Rail and Sea, Smithsonian Institution Reports, 1878.

Repeated attempts have been made to harmonize the facts of color-blindness with the hypotheses outlined in the preceding paragraphs. But, inasmuch as this is almost impossible, it seems permissible to adopt a perfectly empirical classification and to state that one group of color-blind is characterized by an absence of the power to perceive colors, while the other experiences merely a difficulty in distinguishing colors. The first possess achromatopsia and the latter dyschromatopsia, but even the former condition is rarely complete, excepting in cases of definite pathological changes in the optic nerve.¹ Consequently, even the achromatopic person is capable of recognizing one or more fundamental colors. Attention, however, should be called to the fact that the absence of a particular color from the spectrum does not imply that perception of its luminosity has been interfered with. A person may well be able to recognize the spectrum throughout its entire length and yet be unable to distinguish more than two colors, say, red and violet.

Upon the basis of the Helmholtz theory, we may divide color-blindness into blue, green and red-blindness. The most common of these is the *red-blindness*, in which the red end of the spectrum is considerably shortened. A person so afflicted confounds light red colors with dark green and cannot see a dark-red square upon a black background. In fact, the most typical cases show a green-blindness and are capable of distinguishing only the yellows and blues. Consequently, the red, orange yellow, and green appear to them merely as different shades of yellow, while the green is perceived as gray and the indigo, violet, and purple seem blue. A person afflicted with *green-blindness* confounds light-green with dark red and does not recognize a dark green square upon a black background, but can perceive a red square upon black. In many cases, however, they also show a certain interference with the red end of the spectrum and hence, are really green-red blind, although they differ from the red-green blind in certain minor particulars. A person afflicted with *blue-blindness*, sees only red and green and confounds blue with green, purple with red, orange with yellow, and violet with yellow-green. This condition indicates a shortening of the violet end of the spectrum. Blue-blindness of a temporary kind may be produced by the ingestion of santolin.

Color-vision is commonly tested by means of a number of skeins of wool, exhibiting three colors, namely, a pale pure green, a medium purple, and a vivid red (Holmgren). The person suspected to be color-blind is asked to match the pale green skein. If red or green blind, he will recognize this skein as gray with some admixture of yellow or blue and will match it not only with the green skeins but also with those possessing a grayish yellow or blue color. If he is then asked to match the medium purple skein, he will select either

¹ Siven and Wendt, Skand. Archiv für Physiol., xiv, 1903, 196, and Grunert, Archiv für Ophthalm., liii, 1903, 132.

the different purples, the blues and violets, or only the greens and grays. In the first instance, this would signify that he is red-blind, and in the second that he is green-blind. If the red-blind is then asked to match the red skein, he will pick out the greens, grays and browns, possessing a luminosity less than that of the test color, while the green-blind will select the greens, grays and browns of greater luminosity.

PART VII

SECRETION

SECTION XXIV

THE "EXTERNAL" SECRETIONS

CHAPTER LXXVI

THE GROUP OF THE CUTANEOUS SECRETIONS

Classification of the Secretions.—A secretion is a cellular product which is of further use to the body, while an excretion is a cellular product which is of no further use to the body. Obviously, this definition must be held within very general limits, because not all secretions and excretions are fluids. It will also be remembered that the secretions are formed by special colonies of cells which present themselves as "external" and "internal" glands. The former possess a visible duct through which the secretion escapes, while the latter do not, and constitute, therefore, the group of the so-called ductless glands. Consequently, while the "external" secretions are poured upon an open surface of the body, the internal secretions are discharged directly into the blood or lymph stream. For this reason, the former most generally give rise to local reactions, while the latter are distributed throughout the body and aid in the promulgation of physiological processes of a more general and intricate kind. This relatively sharp line of demarcation already drawn between the "external" and "internal" secretions, may be elucidated further by briefly noting the histological character of the glands producing them. The external glands invariably exhibit a structure which betrays its secretory nature almost immediately, while that of the internal glands is generally obscure and cannot readily be associated with secretion.

FIG. 486.—DIAGRAMMATIC REPRESENTATION OF AN ACINUS.

D, Duct; S, secretory cells; L, lymph space; C, blood capillaries.

A secreting mechanism consists essentially of a colony of cells which are arranged around a central cavity or tube for the reception

of their product. The material required for the formation of the secretion, is derived from an intricate system of capillaries situated in the immediate vicinity of their walls. These cells are arranged in groups forming the so-called acini. By combining many of these acini we obtain a lobule. Several lobules constitute a lobe and several lobes the gland as a whole. In general, it may be said that glands are either tubular or racemose in character and may be either simple or compound. As an example of a simple tubular gland, we might mention the sweat glands of the skin or the crypts of Lieberkühn of the small intestine; and as an example of a compound tubular gland, the glands of the pyloric end of the stomach or those of the tongue or uterus. Simple racemose or alveolar glands are those furnishing the sebaceous material for the skin, and compound racemose glands those furnishing the saliva. Some glands, such as the pancreas, are of a mixed type, combining some of the characteristics of the tubular with those of the racemose variety. They are called tubulo-racemose glands.

The Factors Concerned in the Formation of a Secretion.—It was formerly believed that secretions and excretions are the products of a process of filtration. It was conceived that the different cells of the alveoli form a passive membrane, through which the blood plasma percolates from a place of high pressure to a place of low pressure. Obviously, this mechanism may be represented in a plastic manner by adjusting a glass funnel lined with filter paper above a beaker. The solution poured upon this paper takes the place of the blood, because some of its constituents are forced by pressure through the paper into the receptacle underneath. In accordance with the pure *filtration theory*, the differences in the character of secretions are the result of variations in the structure and chemical properties of the dialyzing membrane and not of an active metabolism of its cellular constituents. Later on this theory was modified by the addition of the factors of *osmosis* and *diffusion*, but even in this case, the epithelium remains a passive membrane through which these osmotic interchanges between the blood and the secretion are effected in accordance with ordinary physical laws.

These factors which have been combined by Ludwig and his pupils, into the so-called mechanistic theory of secretion, were soon found to be inadequate, because they failed to explain many of the phenomena connected with this process. Thus, it was found that the histological picture of the resting gland is widely different from that of the active gland, and that in many cases the constituents of the cells could be traced directly into the ducts. This was followed by the discovery of distinct secretory nerves, and lastly, by the observation that glandular processes may also be markedly influenced by chemical means and frequently furnish a product which is not present in the blood. All these data were eventually combined into the so-called *chemical or vitalistic theory* of secretion, the chief advocate of which was Heidenhain.

It is to be emphasized, however, that this chemical theory does not exclude filtration nor osmosis and diffusion as causative factors, but merely states that these processes are modified by certain intracellular reactions, the nature of which is as yet not fully understood. Heidenhain included the latter under the term of vitalism. It is to be clearly understood, however, that this term does not refer to metaphysical phenomena, but simply to a still inexplicable vital activity of the substance of the cells. This implies that the latter do not act merely as passive filters, but influence the secretion by their metabolic changes.

Since the internal secretory organs will be more fully described in a subsequent chapter, the present discussion may be restricted to the "external" secretions. Several of these have already been alluded to in the preceding paragraphs, for example, the cerebro-spinal fluid, the intraocular fluid, the tears and the fatty material of the Meibomian follicles of the eyelids. There still remain to be considered the sweat, the milk, the mucous secretion of the buccal and oral glands, as well as the lymphatic secretions and the very important group of the digestive juices, formed by the saliva, gastric juice, duodenal juice, bile, pancreatic juice and intestinal juice.

The Skin as an Organ of Protection.—The skin consists of the epidermis or cuticle and dermis or cutis vera. The former appears as a layer of stratified epithelium measuring 0.08 to 0.12 mm. in thickness. Its deepest layer or rete Malpighii is composed of protoplasmic nucleated cells, possessing a cylindrical shape. The cells of the surface layer, on the other hand, are hard and horny, non-nucleated, flattened chips which are constantly discharged, their places being taken by new cells arising from the rete Malpighii. While being gradually pushed outward, the latter assume the physical and chemical characteristics of the surface cells. Pigment cells are found in the deeper cells of the epidermis as well as in those of the corium; in the former, however, the pigment is disseminated while in the latter, it is restricted to particular cells. From here this pigment is said to migrate into the more external Malpighian layer, a contention which fully explains the fact that the skin of a white person, grafted to a negro, presently becomes thoroughly pigmented.

With the exception of the palms of the hands, soles of the feet, dorsal surfaces of the last phalanges, glans penis and certain parts of the labia, the skin is beset with larger and smaller hairs. These appendages are epidermal growths contained in the skin pits or hair follicles. The part within the follicles is known as the hair-root. Physically hairs are characterized by their marked elasticity and cohesion, which properties render them capable of supporting a weight of as much as 60 grams. They are very resistant, because composed of a pigmented, horny, fibrous material; and are strongly hygroscopic, a property which explains the painful sensations generally experienced in scars during wet weather. The gradual change in the color of the hairs may be caused either by a diminution in the amount of their pig-

ment or by the presence of minute air-bubbles within their medulla and fibrous layer. These bubbles reflect the light very strongly. The former change is the usual cause of the grayness of the hair in old age, whereas its sudden turning gray is due principally to the formation of these vacuoles.

Physiologically, it is of interest to note that the adult human individual produces about 0.20 gram of hair-substance in the course of a day, but this amount may be greatly increased by heat, massage, and the cutting of the hair. Attention has already been called to the fact that numerous smooth muscle cells lie in relation with the hairs which bridge over the angle formed by the obliquely placed roots of the latter and the surface of the skin. The contraction of these muscle fibers,

therefore, must lead to an erection of the hairs and the peculiar reflex phenomenon, known as "goose flesh." This reaction most commonly arises in consequence of local or general stimuli, such as cold, emotions, and irritations within the domain of the autonomic nervous system. A few cases, however, have been recorded which show that the pilo-motor mechanism may be brought under the control of volition.¹ While the question of whether cats and other animals are able to erect their hairs at will, cannot be decided definitely, it seems that this reaction is not always wholly reflex but embraces a strong element of volition. For the present, however, it must be placed in the group of the perception or association reflexes. The sensitiveness of the hairs which plays so important a part in the sensations of touch, is subserved by a ring-like plexus of nerve fibrils surrounding the hair-follicle.

FIG. 487.—NERVE TERMINALS AROUND THE ROOT OF THE HAIR FOLLICLE.

M, Medulla; *P*, papilla; *E*, external root sheath; *J*, internal root sheath; *N*, ramification of the nerve fiber.

empty directly into the hair-follicles, a means is provided to keep the hairs soft and pliable. In the third place, it should be remembered that these scattered muscle cells play an important part in determining the vascularity of the skin, because their contraction hinders the passive expansion of the capillaries, thereby keeping the blood in the deeper parts of the body, while their relaxation allows the superficial capillaries to become injected with blood drawn from other organs and tissues. Without doubt, these vascular changes possess an important bearing upon the regulation of the body-temperature, because the relaxation of the cutaneous capillaries invariably leads to a greater dissipation of heat, and vice versa. In this connection brief mention should also be made of the fact that the effect of cold and warm baths upon the circulation is made possible in part through these muscle cells, and in part through the muscle cells of the arterioles themselves.

The Skin as an Organ of Secretion.—The *sebaceous glands* are simple acinous in character and are usually found in close relation with

¹ Maxwell, Amer. Jour. of Physiol., vii, 1902, 369.

the roots of the larger hairs. Their ducts open directly into their sheath. But the other regions of the skin are not free from them; in fact, many of them contain them in large numbers, their excretory ducts then opening free upon the surface. They are especially numerous upon the forehead, nose and back; but are absent from the *vola manus* and *planta pedis*. Closely related to these glands are those of the *labia minora*, *glans penis*, and *prepuce* as well as the ceruminous glands of the external auditory meatus. The acini of these structures are packed with polyhedral and flattened cells which divide and gradually move outward in successive layers, where they disintegrate in the oily semi-liquid secretion filling the duct. In this way, a fatty material is formed which on exposure to the air assumes a cheesy consistency. When the ducts of these glands become blocked, this material undergoes retrogressive changes and then forms a fertile medium for the growth of the ordinary pus-microbes.

The exact composition of this secretion is not known. It contains fats, soaps, cholesterin, albuminous material, remnants of epithelial cells and inorganic salts.¹ The cerumen or ear-wax contains a reddish pigment and possesses a bitter-sweet taste. Similar materials are the *smegma præputii* and the fatty and odoriferous secretions of the anal and uropygial glands of many animals. The sebaceous material which is generally found upon the skin of the newborn infant, is known as *vernix caseosa*.² Its distribution alone would indicate that it possesses a manifold function. Thus, it may rightly be concluded that it serves to lubricate the surface of the skin and to protect the hairs against drying. Moreover, since it is spread out in an almost continuous layer across the skin, it aids in retaining the body-heat and plays, therefore, an important part in regulating the body-temperature. This fact is clearly recognized by the northern races, such as the Esquimaux, because they carefully preserve this secretion and even intensify its action by anointing their bodies with fatty substances. In the aquatic animals it serves a twofold purpose, because it protects them against any undue loss of heat and diminishes the friction between their integument and the water. Lastly, the modified secretions of the anal, uropygial, and sexual glands of many animals no doubt play an important part in the production of the sexual reflexes.

The *sweat-glands* are simple tubular in character and consist of a coiled up portion which occupies the deeper layer of the skin, and a long winding duct which penetrates the corium and epidermis and eventually terminates in a funnel-shaped enlargement upon its surface.³ They are found in especially large numbers upon the palms of the hands, the soles of the feet, in the axilla, groin and upon the forehead, but are absent from the *glans penis*, *prepuce* and the margins of the

¹ Linser Dissertation, Tübingen, 1904.

² Zumbusch, Zeitschr., ph. Chemie, LIX, 1909, 506.

³ Rabl (Histology of the Sweat-Glands) in Handb. der Hautkrankheiten, Wien, 1901.

lips. Their number has been estimated at two millions¹ and their total secretory surface at 1080 m². The cells lining the coiled up extremity of these glands are columnar in shape and possess a granular cytoplasm. Externally they border upon a dense network of capillaries.

The sweat is a clear, colorless liquid of low specific gravity (1.004). It consists of 982 parts of water per 1000 c.c.; and contains small quantities of salts, neutral fats, volatile fatty acids, and traces of proteins and urea. The inorganic salts include sodium chlorid and small quantities of alkaline sulphates and phosphates. The latter impart to it a faint alkaline reaction, although when first secreted it is prone to be acid, owing to the presence of a slight amount of sebaceous material. Profuse sweating, however, may yield other proteins, such as uric acid, creatinin, ethereal sulphates, phenol, skatol, and albumin.² Consequently, sweating is called for whenever the activity of the kidneys is temporarily suppressed. Muscular exercise also tends to augment the urea content of the sweat, and in addition, gives rise to an elimination of CO₂ which may amount to as much as 20 grams per day. Under normal conditions, however, the secretion of sweat serves merely as a means of eliminating water and not of solid excrements. While this fact may be regarded as sufficient reason to classify sweat as an excretion, the use made of it subsequently in moistening the surface of the body and in regulating the body-temperature, may prompt us to consider it as a secretion.

FIG. 488.—DIAGRAMMATIC REPRESENTATION OF THE SKIN, SHOWING THE LOCATION OF THE SWEAT GLANDS.

H, Horny layer; L, stratum lucidum; M, Malpighian layer; P, corpuscles of Pacini; PL, papillae of the cutis vera; C, cutis vera; S, sweat gland; SC, subcutaneous tissue.

while the remainder forming the so-called visible sweat, is absorbed by the clothing or is lost in mass. Naturally, a moisture-laden atmosphere retards the evaporation and tends to produce a much larger quantity of visible sweat than a dry and warm atmosphere. It should also be remembered that the secretion of sweat is closely correlated with that of urine, because copious sweating most generally diminishes

The small quantity of sweat generally produced, evaporates and leaves non-volatile constituents upon the skin,³ but naturally, its total quantity differs greatly with the general condition of the body and the surroundings. A person dressed moderately warm may secrete as much as 2 or 3 liters in a day, although an outside temperature which causes the temperature of the skin to rise above 33°C., yields a much larger quantity. A part of this may be removed by evaporation,

¹ Krause, *Handb. der Anatomie*, 1879.

² Brieger and Dieselhorst, *Deutsch. med. Wochenschr.*, xxx, 1904, 161.

³ Schierbeck, *Archiv für Anat. und Physiol.*, 1893, 116.

the elimination of water by the kidneys, and vice versa. Both of these processes are related in turn to the intestinal secretions, because watery stools are invariably associated with a diminished excretion of water by the other channels.

The Innervation of the Sweat-Glands.—The sweat-glands are richly supplied with nerve fibers, some of which are doubtlessly secretory in their nature. They perforate the *membrana propria* and form mulberry-like end-organs directly upon the outer surfaces of the cells. According to Langley,¹ those innervating the glands of the cat's hind limb leave the spinal cord in the first and second lumbar nerves, enter the sympathetic system and leave it again in the gray rami of the sixth lumbar to the second sacral nerves. Their chief outpouring takes place in the seventh lumbar and first sacral rami. All of them enter into the formation of the sciatic plexus. A similar outpouring occurs between the fourth and tenth thoracic nerves, the fibers of which eventually enter the brachial plexus.

The presence of these secretory fibers has been demonstrated by Goltz² who stimulated the distal end of the divided sciatic nerve and observed drops of sweat appearing upon the hairless skin covering the balls of the feet. This effect may also be evoked after the ligation of the abdominal aorta as well as after the amputation of the leg, but naturally, only a very limited amount can then be obtained, because the cells are no longer able to acquire new secretory material. Under normal conditions, this nervous mechanism is activated by rises in the temperature of the atmosphere as well as by increases in the blood-pressure following muscular activity and increases in the water content of the body. Furthermore, many factors are constantly at work which tend to vary the amount and character of this secretion. It is a well known fact that the skin in fever is dry and that the subsequent reappearance of the sweat is generally accompanied by a fall in the body-temperature. In other words, a moist skin is a favorable diagnostic sign, because it facilitates heat-dissipation. Profuse sweating is frequently associated with dyspnea, nausea and psychic impressions of terror. Among the drugs which influence the character of this secretion should be mentioned pilocarpin and atropin. The former stimulates its flow by acting directly upon the terminals of the secretory nerves, while the latter diminishes it by paralyzing these endings. Alcohol produces a dry skin and nicotine a moist skin. Cold lessens the secretion, because it gives rise to a reflex constriction of the cutaneous blood-vessels.

The Mammary Glands.—Each fully formed mamma consists of 15 to 20 lobes, which are composed of lobules and the latter in turn of numerous groups of cells or acini. The smaller ducts emerging from these eventually unite into a large lactiferous duct which opens through the nipple. Externally to their point of union the different

¹ Jour. of Physiol., xii, 1891, 347.

² Pflüger's Archiv, xi, 1875, 71.

lobular ducts are enlarged into sinus-like reservoirs, which may become highly distended during the periods of active secretion of this gland. The orifice of the lactiferous duct is invested by areolar tissue and smooth muscle fibers, the latter effecting the erection of the nipple on reflex stimulation. Around its base winds a narrow zone of dark-tinted skin which is beset with very sensitive papillæ and contains numerous minute secretory glands of the sebaceous type. Although doubtlessly belonging to the group of the cutaneous glands, it is difficult to classify the mammæ either as modified sweat-glands or as sebaceous glands. Their alveolar character as well as the fatty character of their secretion, might prompt us to homologize them with the latter, but since their secretory cells are short columnar in outline and are arranged in a single row, they really present a much closer resemblance to the former. Their size, number, and position vary greatly in different mammals. In man, they are placed one upon each side of the anterior aspect of the thorax and are copiously supplied with blood-vessels, lymphatics and nerves.

The histological character of these glands varies considerably and especially during pregnancy and lactation. When milk is first formed, the epithelium of the alveoli becomes sharply differentiated from that of the ducts. While the lining of the latter remains cuboidal in shape, that of the former becomes elongated toward the lumen, and shows a proliferation of the nuclei as well as numerous new granules and fat-globules. This state is soon followed by one of active secretion. The cells then enlarge still further and project markedly into the lumen of the acini. Fat-droplets now appear in much greater numbers, while the granules which during the early secretory period presented a spherical outline, are now elongated and spiral in shape.¹ A part of the inner segment of each cell then disintegrates, its fragments being forced into the duct. This fully explains the fact that the early secretion invariably embraces many epithelial cells which are only partly transformed, and are, therefore, known as colostrum corpuscles.² The places previously occupied by these fragmented cells, are again taken up by new ones formed by karyokinetic division from neighboring cells. In many cases, however, the ruptured inner part of the cell is again closed, whereupon the cytoplasm is slowly reformed.

During pregnancy, the mammæ enlarge and become firm and tender to the touch. Their blood-supply then increases enormously, as is evinced particularly by the formation of prominent plexuses of veins. The areola investing the base of the nipple, becomes broader and darker in color and shows very prominent papillæ. The nipple itself increases materially in size. Evidently, these macroscopic changes find their origin in a gradual proliferation of the secretory cells and the formation of many new acini. This process of evolution begins soon after conception and does not cease until shortly after

¹ Steinhaus, *Archiv für Physiol.*, 1892, 54.

² Heidenhain, *Hermann's Handb. der Physiol.*, 1883.

the birth of the young. The flow of milk, however, does not commence as a rule until labor has been completed; in fact, in woman it does not begin until 24 or 48 hours afterward, but its onset may be considerably hastened by the mechanical stimulation of the mammae. In woman the duration of the period of lactation varies from a few days to almost a year, but much depends upon their general condition and the stimuli to which they have been subjected. Inasmuch as the onset of a new pregnancy brings this secretion to a close, lactation is frequently made to continue by artificial means in order to prevent a new conception, but this practice fails in most instances to have the desired effect. Lactation having been completed, the glands involute, *i.e.*, they undergo retrogressive changes which finally lead to the establishment of the normal histological picture of the resting organ.

The Innervation of the Mammary Glands.—Since the mammary glands do not seem to be in possession of secretory nerves, we cannot help being astounded at the close adaptation of the activity of these organs to the condition of the developing young. Thus, we find that the mammae begin to grow very shortly after conception and continue their growth until the birth of the young. With surprising exactitude the milk pours forth, not to cease until the end of the period lactation, *i.e.*, about six to nine months thereafter. The only condition for it is to remove it regularly—preferably in a normal way by the process of suckling. Obviously, we are dealing here with a most remarkable transfer of function, because while the fetus abstracts its nutritive material directly from the mother's blood with the help of the placenta, the infant derives its nutritive material entirely from the mammae. But this change is not at all detrimental to the young, because milk is a preparation which is accurately adapted to its assimilative and dissimilative power.

The progressive character of the development of the mammae suggests that it is controlled by some mechanism which in turn is influenced by the sexual organs. Regarding this point, we have the positive experimental evidence that extracts of corpus luteum of the ovary and of the developing uterus give rise to an active growth of the mammae even in non-pregnant animals.¹ Secondly, we shall see later that the internal secretion of the pituitary body possesses a pronounced excitatory influence upon the flow of milk, but while it seems to have been definitely established that the acquisition of the full functional power of the mammae is controlled by chemical stimuli of the type of the hormones, it cannot be denied that a reflex nervous factor is at work. Thus, it has been found that the stimulation of sensory nerves is followed by a diminution in the amount of this secretion and that, in woman, the period of lactation may be cut short by strong emotions, epileptic seizures, and other general functional disturbances. Moreover, this influence may be reciprocal, because the artificial suppression of this secretion may have deleterious effects upon

¹ Lane-Claypon and Starling, *Proc. R. Soc.*, 1906, and Hammond, *ibid.*, 1917.

the health of the woman. In this connection, it is also of interest to note that the act of suckling excites tonic contractions of the uterus, a means commonly employed to cause this organ to assume its former shape after labor, and especially when this involution is slow and is associated with hemorrhage. It should also be noted that the secretion of milk is not exclusively a function of the pregnant female, because many cases are on record of men and boys possessing well developed and actively secreting mammæ. It had also been observed that virgin bitches may produce milk and that sterile mules may yield sufficient milk to suckle a foal.

Properties of Milk.—When the mammæ first begin to discharge their secretion, they do not yield pure milk but a peculiar fluid which is known as *colostrum*. A few drops of this secretion may usually be obtained within a short time after the completion of labor by gently massaging the breasts in the direction of the nipples. Its total amount, however, is never considerable although it flows more freely later on. As has been stated above, this material is gradually flushed out of the ducts, giving way in the course of two or three days to pure milk. To begin with, the colostrum appears as drops of a watery and usually very cloudy fluid, possessing a specific gravity of 1.040 to 1.080. In larger quantities it exhibits an opalescent, yellowish appearance, and gives rise to a coagulum of similar color. The pigment to which the latter is due, is contained in its fatty admixtures. When examined under the microscope, it is seen to contain numerous fat-globules and fragmented cells, among which are many leukocytes which have migrated and have become loaded with fat-droplets. Colostrum yields little or no casein but about 3 per cent. of proteins, consisting of coagulable lactalbumin and lactoglobulin. Moreover, while it contains as much fat as the pure milk secreted subsequently, it embraces somewhat greater quantities of lactose and salts. Colostrum is nature's laxative, and hence, the infant should be allowed to partake of it freely.

The milk, following the colostrum, is an opaque fluid, possessing a yellowish white or bluish white appearance according to its concentration. It possesses a sweetish taste and a very characteristic odor. Its specific gravity varies between 1.026 and 1.036, the highest values being generally obtained only in well nourished women. It is neutral to litmus, alkaline to lacmoid, and acid to phenolphthalein. When examined under the microscope, it is seen to consist of a watery part, or milk-plasma and numerous fat-globules, or milk-corpuscles. The diameter of the latter varies between 1μ and 6μ . Here and there we also recognize fragmented epithelial cells, leukocytes and nuclear material. Milk, therefore, is essentially an emulsion of fat, the opaque appearance of which is due to the diffuse reflection of the light by these globules. On standing, these droplets of fat rise to the surface, owing to their lesser specific gravity, and form the *cream*. By mechanical agitation the latter may be made to coalesce to form *butter*. This fact, that it requires agitation to coalesce the fat-globules, has been the subject of much study. Thus, it has been shown that the globules in cow's milk are invested by a mucous-like envelope, which must first be broken up before the fat can run together. In addition, it has been assumed that the globules in other types of milk are surrounded by a haptogen membrane which is formed of the proteins of the

cell from which they have been derived, but it seems scarcely necessary to make this assumption, because such an investment might more easily result in consequence of the molecular attraction of the fat for the neighboring protein particles.¹

If milk is boiled, a "*skin*" is formed upon its surface, which consists of lactalbumin, casein and calcium salts. Furthermore, when exposed to the air, milk undergoes a peculiar fermentation in consequence of the entrance of micro-organisms, chief among which is the *bacillus lacticus*. Its reaction then changes to sour, owing to the formation of lactic acid from lactose. Milk may also undergo *alcoholic fermentation*. While this change is not easily effected by means of yeast cells, it is readily brought about by fungoid growths. The milk-sugar is converted into glucose and galactose and the latter into alcohol and carbonic acid. In this way, such preparations as Koumiss and Kephir have been derived. The *coagulation of milk* is usually brought about by means of rennin, an enzyme contained in the gastric juice of mammals. The clot, or *curd*, consists of casein and entangled fat-droplets, while the fluid residue, or *whey*, embraces sugar, salts, albumin and a newly-formed protein called whey-protein.

The Composition of Milk.—The formation of milk depends not only upon the condition of the mother but also upon that of the infant. A robust woman, especially a multipara, may yield a large enough quantity to feed half a dozen infants, but naturally, the true physiological measure is the amount which is required for the welfare of a single infant, weighing, say, 3000 to 3500 grams. These requirements are compiled in the succeeding table:

Required by infant	1 day.....	20 grams
	2 days.....	75 grams
	3 days.....	168 grams
	4 days.....	252 grams
	5 days.....	303 grams
	6 days.....	353 grams
	7 days.....	367 grams
	2 weeks.....	472 grams
	3 weeks.....	512 grams
	4 weeks.....	512 grams
	5 weeks.....	577 grams
	6 weeks.....	613 grams
	7 weeks.....	691 grams

A comparison of these data with those now following shows conclusively that the average woman furnishes an ample supply of milk, and that the quantity secreted increases steadily as demanded by the growth of the infant, until about the 28th week, when its amount diminishes up to the end of the period of lactation.

Secreted by mother	1 day.....	20 grams
	2 days.....	97 grams
	3 days.....	211 grams
	4 days.....	326 grams
	5 days.....	364 grams
	6 days.....	402 grams
	7 days.....	478 grams
	1 week.....	502 grams

¹ Hammarsten, Lehrb. der physiol. Chemie, 1907, und Raudnitz, Ergebn. der Physiol, ii, 1903.

Secreted by mother	3-4 weeks.....	572 grams
	5-8 weeks.....	736 grams
	9-12 weeks.....	797 grams
	13-16 weeks.....	836 grams
	17-20 weeks.....	867 grams
	21-24 weeks.....	944 grams
	25-28 weeks.....	964 grams
	29-32 weeks.....	916 grams
	33-36 weeks.....	909 grams
	37 weeks.....	885 grams

The *fats* of milk are similar to those contained in adipose tissue. Their proportion may be given as follows: olein, $\frac{3}{7}$, palmitin, $\frac{1}{8}$; stearin, $\frac{1}{6}$; butyrin, caproin, and caprylin, $\frac{1}{4}$. In milk-plasma are found various proteins, a carbohydrate, lactose, inorganic salts and a small amount of lecithin and nitrogenous extractives. The principal *protein* is called caseinogen. It belongs to the group of the phosphoproteins and may be precipitated by acids, such as acetic acid, or by saturation with magnesium sulphate, or half-saturation with ammonium sulphate. Rennin causes it to coagulate with the formation of casein. This process is employed in the preparation of cheese, the curd consisting of casein and entangled fat-globules. If this coagulated mass is allowed to stand, milk-serum separates from it. The latter contains two other proteins, namely, lactalbumin and lactoglobulin. The *carbohydrate* is milk-sugar or lactose, a disaccharide of the composition: $C_{12}H_{22}O_{11}$. When hydrolized it takes up water and galactose:

It may be also be found in the urine of woman during the early days of lactation, when there is a reabsorption of the lactose owing to an insufficient withdrawal of the milk. For the same reason, it may enter the urine during and after the period of weaning. It then gives the ordinary tests for reducing sugar. The *salts* of milk consist of calcium phosphate, a small quantity of magnesium phosphate and the chlorids of sodium and potassium. Especially marked is the richness of milk in calcium, phosphorus, and magnesium, as compared with the blood-serum. This is of greatest importance for the growth of the bones, while the growth of the tissues necessitates potassium rather than sodium. At all events, it is a most striking fact that these cells are capable of selecting from the fluids of the body only those salts which are of greatest use to the developing young. This selective action they also display in the formation of caseinogen and lactose, both of which do not exist as such in the blood or lymph. It is by means of this concentration of materials of the proper kind that the rabbit is enabled to double its weight in six days, the dog in 96 days, and the infant in 108 days.

The practical importance of these brief chemical data becomes apparent immediately if a substitute must be sought for human milk.¹ Although other types of milk are more like human milk, we are then accustomed to use cow's milk, because it is most easily procured. Its composition, however, is very unlike that of human milk, as the following tabulation will show:

	Human	Cow's
Water.....	87.16	87.10
Fat.....	4.28	4.20
Casein.....	1.04	3.25
Sugar.....	7.40	5.00
Ash.....	0.10	0.52

¹ Völtz, in Oppenheimer's Handb. der Biochemie, 1910, iii, 382.

The most important differences may be briefly summarized as follows:

(a) Appearance. Cow's milk is white in color and opaque, while human milk is more translucent and possesses a yellowish or bluish hue in accordance with its concentration.

(b) Reaction. Cow's milk is acid, while human milk is alkaline,

(c) Specific gravity. Cow's milk: 1.030–1.035; human milk: 1.024–1.035,

(d) Character of the curd. Rennet produces with cow's milk a dense and firm coagulum which is not easily digested, while human milk yields under the same circumstances a light, flocculent and easily digestible clot.

(e) Histological character. The fat-globules of cow's milk are invested by a relatively thick albuminous envelope.

(f) Bacteriological character. Human milk is in a practically sterile condition when withdrawn from the breast.

These differences in the chemical composition and reaction must first be removed by diluting cow's milk to reduce the casein and by adding to it cream and milk-sugar, making the whole alkaline in reaction. The danger of microbic infection of cow's milk may be obviated by pasteurization, *i.e.*, by subjecting the milk to a temperature of 167–175°F. which sterilizes it, but does not impair its nutritive value. The following formula may be employed as a sample:

Top milk.....	5 drams
Water.....	5 drams
Lime water.....	1 dram
Sugar of milk.....	20 grains

But this "humanized" cow's milk cannot be regarded as a perfect substitute for natural mother's milk. Undoubtedly, there are also certain other differences present which the chemist has not detected as yet. As one of these might be mentioned the qualitative differences between the caseinogen of different types of milk.

CHAPTER LXXVII

THE LYMPHATIC AND MUCOUS SECRETIONS

The Spleen.—Since this organ possesses the characteristics of lymphatic tissue and has not been proved to furnish an internal secretion, it may properly be considered under the heading of the lymphatic glands. It is, of course, a ductless organ and belongs to the group of the hemal bodies which are distinguished from the ordinary lymphatic glands by their red color and by the fact that their sinuses contain only blood. Histologically it is of importance for us to remember that it is enveloped by a capsule of fibrous tissue, containing elastic fibers and smooth muscle cells. Numerous septa or trabeculae extend from its inner surface into the interior of the organ which they

subdivide into compartments containing the spleen pulp. The latter is dark red or reddish-brown in color and is composed chiefly of cells embedded in a ground substance of fibers and the prolongations of large nucleated cells. Some of the latter greatly resemble lymph-corpuscles, while others contain a pigment which is closely allied to the hemoglobin of the red blood corpuscles. Scattered through the pulp are many red corpuscles and the fragments derived from them. The blood-vessels enter and leave this gland at the hilus and remain at first confined to the trabeculæ. Eventually, however, they terminate in a network of capillaries in the pulp, their endothelial lining becoming continuous with that of the rete of the latter. The sheaths of these minute arteries are beset with rounded bodies, the so-called Malpighian corpuscles, the structure of which is practically identical with that of a lymph nodule. The veins also begin as opened tubules. Consequently, it will be seen that the cellular elements of the splenic pulp are in actual contact with the blood and not with the lymph, as is the case in other organs. This arrangement enables the blood to be poured out directly into the interstitial spaces of this organ.

The Function of the Spleen.—Since the removal of this organ is not followed by serious consequences, the conclusion seems justified that it does not furnish an internal secretion which is essential to life. In fact, the symptoms of splenectomy are transient in their nature and betray themselves in an anemia, a greater cholesterol content of the blood, and a greater resistance to hemolytic agents.¹ Furthermore, it is possible to transplant this organ into the subcutaneous tissues, but the growth of these transplants is not assured, unless the animal is still young and is not in possession of left-over splenic tissue. In other words, the transplanted portion is more prone to degenerate if a portion of the spleen has been left in the body or if the animal has reached a stage of its life when the function of this organ is no longer absolutely essential, because its loss may then be more easily compensated for by the other lymphatic tissues.² These facts strongly point toward the presence of a hormone which stimulates the growth of the transplant.

In the absence of more positive results following the removal of this organ and in view of its characteristic lymphatic structure, it may be assumed that it is engaged in the formation of white blood corpuscles. This assumption is correct, because it has been shown that the blood of the splenic vein contains large numbers of lymphocytes. Secondly, it is a well-known fact that the disease, known as leucocythemia, in which the number of the white cells is greatly increased, is invariably associated with an enlargement or hypertrophy of this organ. Large numbers of these cells may then be released from his organ by causing it to contract by means of an electric current applied to the neighboring abdominal wall.

¹ Karsner and Pearce, *Journ. Exp. Med.*, xvi, 1912, 769.

² Manely and Marine, *Jour. Exp. Med.* xxv, 1917, 619.

It has also been established that in embryonal life the spleen possesses the function of a hematopoietic organ and that its power of forming corpuscles may be called into play during adult life whenever required. In fact, it seems to retain this function during the entire life of some animals, because it embraces cells which display all the characteristics of the hematoblasts of the bone marrow. In these animals, the removal of the spleen gives rise to a hypertrophy of the bone marrow.

The spleen is one of the organs in which the red corpuscles of the blood undergo disintegration. This inference is based upon the fact that the pulp contains an abundance of these cells in varying stages of degeneration. This statement, however, is not meant to imply that this organ is the chief place in which the red corpuscles are destroyed, nor that their disintegration actually leads to a liberation of their coloring material, the hemoglobin. More plausible is the view which holds that the spleen merely accomplishes the fragmentation of the worn out corpuscles which are then more fully reduced in the liver. Under pathological conditions, however, its destructive power may be greatly increased, as is proved by the fact that it then becomes a depository for iron which can only be derived from the red corpuscles. Such a condition is developed in the course of the disease, known as pernicious anemia. It has also been demonstrated that the spleen aids in the formation of uric acid, because the removal of the kidneys gives rise to an accumulation of this substance within this organ.

Attention has previously been called to the spongy character of the pulp of the spleen which enables this organ to accommodate enormous quantities of blood. With the help of the smooth musculature of its capsule and trabeculæ, this blood is again returned into the general circulation. For this reason, it may be conjectured that this organ acts as a vascular reservoir or diverticulum for the digestive organs or the portal circulation. Its smooth musculature is innervated by fibers which closely invest the splenic arteries and are derived from the celiac ganglion of the solar plexus. In this way, the spleen is brought into correlation not only with the other portal organs but also with the central nervous system. Stimulation of these nerves evokes a vaso-constrictor reaction which prevents the arterial blood from entering the spleen, while its venous tubules are emptied. The division of these nerves, on the other hand, gives rise to an engorgement of this organ and a withdrawal of a considerable quantity of blood from the general circulation. Of special interest is the fact that these alterations in its vascularity may also result in consequence of reflex stimulation; in fact, Roy¹ and others state that they appear with almost rhythmic regularity at the rate of one in about every minute. Since the mechanical effect of these ordinary wave-like contractions upon the general circulation cannot be considerable, they must be more

¹ Jour. of Physiol., iii, 1881, 203, also Schaefer and Moore, Jour. of Physiol., xx, 1896.

especially concerned with a periodic renewal of the blood filling the splenic spaces.

The Tonsils.—The faucial tonsils consist of two globular masses of lymphoid tissue placed in the recesses between the palatal arches. Although originally developed in two lobes, an upper and a lower, this demarcation disappears shortly before birth and the entire organ then appears as a nearly spherical, slightly flattened disc which is attached to the floor of the tonsillar sinus by a root consisting of tonsillar tissue and a fibrous investment. The latter, in fact, spreads over its entire attached surface and becomes continuous with the fibrous layer of the neighboring mucous membrane. A number of membranous septa extend from its surface into the substance of this organ, subdividing it into a number of lobules. Its outer surface is covered with epithelium.

The crypts of the tonsil may be single or branched. In the former case, they retain a rather uniform diameter throughout their course, while in the latter, their outer portions are much narrower than their inner. They are directed, as a rule, in a straight line toward the surface and show no contents with the exception of irregular accumulations of cellular débris. Consequently, the capsule of the tonsil with its trabeculæ forms an inverted replica of the epithelium in which are situated the blind ends of the crypts. A thin layer of lymphoid tissue surrounds their basal portions, whence it extends outward and divides the different crypts into several colonies.¹

The Function of the Faucial Tonsils.—The tonsils reach their highest development in the mammals in which they show a steady growth early in life. They atrophy later on. Regarding their function we know little, the only definite conclusion being that they play the part of a hematopoietic tissue. This inference seems justified in view of their lymphoid structure. Many of the lymphocytes produced in the germinal centers of their follicles find their way through the epithelium into the crypts, where they help in the formation of the cheesy masses so often found in these ducts. A certain number of them also enter the general efferent lymphatics of the neck. It is a suggestive fact that the tonsil attains its greatest activity during the early years of life, when the body is still growing and is greatly in need of large numbers of white corpuscles. It will be remembered that the other lymphoid nodules are at this time similarly active. Consequently, the tonsils merely participate in a general function and the part played by them may readily be compensated for by other lymphoid tissues. These facts tend to show that a mild degree of hypertrophy of the tonsils is to be expected in early youth and that the removal of these organs should not be advocated unless their size and condition leads to such symptoms as impaired breathing, and an interference with the voice and movability of the palate.

The preceding deduction may be employed as a means of disposing

¹ Barnes, *The Tonsils, Faucial, Lingual and Pharyngeal*, St. Louis, 1914.

of the assumption that the tonsils give rise to an internal secretion.¹ The fact that the now extensively practised enucleation of these organs does not produce untoward symptoms should be sufficient to prove this point. Those investigators who nevertheless adhere to the contrary contention, must admit that this secretion cannot be specific, but must be common to all the lymphoid tissues so that the activity of the tonsils may be compensated for by other structures. A third contention is that these organs protect the organism against bacterial invasion. This assumption is in accordance with the general conception that lymphoid nodules act as sieves and catch the infectious particles in their meshes. While it cannot be denied that the tonsils possess an influence of this kind, it is also true that they form a relatively open connection between the cavity of the mouth and the lymphatics of the neck and may, therefore, rather invite infection than prevent it. In fact, tonsillectomy is frequently practised to do away with this possible source and path of infection, and especially if these organs have been the seat of inflammation (tonsillitis) and are in part disintegrated. These cases are usually benefited by tonsillectomy, but naturally, this is not a sufficient reason to condemn the tonsils as perfectly useless organs and to advocate their removal as soon as they rise above the margins of the faucial pillars.

The Lingual and Pharyngeal Tonsils.—The lingual tonsil consists of a variable number of lymphoid nodules arranged along the base of the tongue next to the median line. The pharyngeal tonsil or adenoid is a similar mass of lymphoid tissue which is suspended from the vault of the naso-pharynx immediately behind the nasal choanæ. Smaller depositions are found upon the posterior and lateral walls of the pharynx. Their histological character is practically identical with that of the faucial tonsil, and so is their function.

The Mucous Glands and Their Secretory Product.—A large number of small glandular bodies are found in the mouth and alimentary canal which furnish a very viscous and stringy secretion. This quality is imparted to it by a special constituent, the mucin. In accordance with their distribution, these glands may be classified as buccal, palatinal and lingual. Their structure is practically identical with that of a simple tubular gland, possessing large and clear lining cells. Obviously, the function of this viscous secretion is to lubricate the mucous surfaces.

A very good illustration of the action of a mucous gland is furnished

FIG. 489.—GOBLET CELLS SHOWING THE ACCUMULATION AND DISCHARGE OF THE MUCOUS MATERIAL.

¹ Massini, *Int. Secretion of the Tonsil*, New York Med. Jour., 1898, and Scheier, *Berliner Laryngol. Gesellsch.*, 1903.

by the goblet cells with which the epithelial lining of the intestine is equipped. Scattered among the ordinary reticular cells are some which undergo constant alterations in their size and shape. Originally columnar in outline, they are slowly elongated, because their cytoplasm gradually increases until their free ends project beyond the general surface of the mucosa. The internal tension having reached its physiological limit, their inner walls rupture, allowing a large part of their contents to escape into the intestinal lumen. Being still in possession of its nucleus, the partially emptied cell forms new material and closes the defect in its wall. Many of these cells, however, go to pieces, their places being taken by cells hitherto dormant. The material which is in this way extruded into the intestinal canal contains large amounts of mucin, the purpose of which is to lubricate the mucosa. This is of especial value in the large intestine in which the fecal material becomes partially hardened on account of an absorption of a considerable portion of its water. In this particular segment of the alimentary canal, the ordinary goblet cells are augmented by the modified cells of the crypts of Lieberkühn. It will be pointed out later on that these crypts possess a true secretory power only in the small intestine and become ordinary mucous glands in the large intestine.

CHAPTER LXXVIII

THE DIGESTIVE SECRETIONS

A. SALIVA

The Salivary Glands.—Heidenhain recognized two types of glands, namely, the mucous and the albuminous or serous. Strictly speaking, this classification is not quite correct, because even the simple mucous glands of the oral mucosa furnish at least some albuminous material, while traces of mucin are also found in the albuminous salivary glands. The first of the digestive secretions is the saliva. It is supplied by the so-called salivary glands of which there are six in all, namely, two parotid, two submaxillary and two sublingual glands. Since these organs are paired, it suffices to state that the first lies above the ramus of the lower maxillary bone, while the last two occupy positions upon the floor of the mouth in close proximity to the angle of the jaw. It is true, however, that the arrangement of these glands differs somewhat in different animals. In the dog and cat, for example, the sublingual is wanting entirely, its function being transferred to the so-called retro-lingual gland which is situated somewhat nearer the angle of the jaw. In the pig, all three basal glands are present, *i.e.*, the submaxillary, retro-lingual and sublingual. Traces of the second are sometimes found in man, in addition to the three just enumerated.

These anatomical variations are associated with very striking histological differences as well as with differences in the character of the secretion. Naturally, the saliva obtained from the mouth is a mixed secretion, because it is derived from three sources, namely: (a) from Stenson's duct which drains the parotid gland and opens upon the inner surface of the cheek opposite the second molar tooth, (b) from Wharton's duct which conveys the submaxillary secretion into the groove next to the frenulum of the tongue, and (c) from the ducts of Rivinus which drain the sublingual gland. The latter are multiple and may form as many as twenty different tubules. In the dog, one of them most generally attains a considerable caliber and pursues a course parallel to Wharton's duct. It is known as the duct of Bartholin. While the chemical characteristics of saliva will be dealt with in a later chapter, it may be stated at this time that the parotid secretion is clear serous in character, while that of the sublingual gland is very viscous and stringy. The submaxillary furnishes a secretion which displays intermediate qualities.

The Histological Character of the Salivary Glands.¹—Each gland is made up of lobes and lobules, and each lobule in turn of numerous groups of tubulo-saccular alveoli or acini. Each acinus consists of a number of large and rather square cells which surround the inner extremity of every small duct. The appearance of these so-called chief cells varies with the character of the secretion. In the fresh state, those forming the mucous glands, such as the sublingual, contain large granules of mucinogen which is the precursor of mucin. In the fixed state, on the other hand, these cells appear swollen, the center of their clear cytoplasm being occupied by a well differentiated rounded nucleus. In many of these mucous glands, such as the submaxillary of the dog and cat, the different alveoli of chief cells are invested by crescentic groups of marginal cells which stain deeply and contain no mucinogen. These formations are the demilune cells or crescents of Gianuzzi. Other glands present a mixed character and embrace acini composed of mucous cells right beside those made up of albuminous cells. This is true not only of the submaxillary gland of man in which the serous cells predominate, but also of the sublingual gland, in which the mucous cells are more numerous. In the rabbit, the submaxillary presents the characteristics of a serous gland and the sublingual those of a mucous gland. It need scarcely be mentioned that these structural peculiarities are associated with corresponding differences in the character of the saliva.

Such glands as the parotid, and in part also the submaxillary, furnish a watery and non-viscid secretion. Their chief cells are filled with small granules of an albuminous type which constitute the mother-substance of the active principle of the saliva, called ptyalin. Upon it depends the digestive power of this secretion. While resting in the cells these granules are designated as zymogen granules, or ptyalin-

¹ R. Metzner, in Nagel's Handb. der Physiol., Braunschweig, 1907.

ogen. They remain inactive until discharged into the ducts, when they are immediately converted into the active enzyme ptyalin.

Histological Changes During Activity.—A most interesting feature of the activity of glands is that they undergo certain very characteristic changes in their structure. While this is true of the lacrimal, gastric and pancreatic glands, none exhibit them in a more striking manner than the salivary glands. They were first studied by Heidenhain¹ in fixed and stained preparations of the parotid and submaxillary glands of the rabbit, but have also been observed by Langley² and others in fresh preparations. When resting these cells are large and faintly outlined against one another by delicate cell walls. Their cytoplasm is evenly packed with granules which stain deeply with the ordinary dyes. Near the basement membrane are found their somewhat irregular and dark nuclei. Contrary to this picture, a cell which has been made to secrete for a considerable length of time, is smaller, more

FIG. 490.—ACINI OF THE SUBMAXILLARY GLAND DURING REST (R) AND ACTIVITY (A). THE DARK OUTER CELLS REPRESENT THE DEMILUNE CELLS.

translucent, and contains a rounded nucleus which occupies a position near its center. Many of these cells, in fact, appear merely as a narrow frame of cytoplasm, investing a very prominent rounded nucleus. The granular material has disappeared from the entire inner part of the cell and is now arranged in the form of a narrow zone along its margin next to the duct.

These changes clearly prove that these cells lose a certain part of their substance in the course of their activity; in fact, Heidenhain states that many of them disappear altogether, but reform their contents during the subsequent period of rest. Of special interest is the fact that the active cell gradually discharges its zymogen granules which, as has been mentioned above, give rise to the enzyme ptyalin. Upon the cessation of this stimulation, the stage of dissimulation is followed immediately by a stage of assimilation during which the material lost is again replenished. A clear non-granular material is then seen to invade the basal segment of the cell which is gradually

¹ Noll, *Ergebn. der Physiol.*, iv, 1905.

² *Jour. of Physiol.*, x, 1889, 433.

converted into the granular substance so clearly betrayed by the resting cell. In the mucous cells it has been observed that their large granules swell up and disappear, probably in consequence of an inhibition of water which causes the mucinogen to be converted into mucin. The fact that salivary secretion is associated with such pronounced histological changes cannot surprise us, if it is remembered that the submaxillary gland of the dog secretes its own weight as saliva in the course of five minutes and is able to continue this process for many hours.

The Paralytic Secretion of Saliva.—It has been found by Cl. Bernard (1864) that the division of the chorda tympani innervating the submaxillary gland, gives rise to a continuous secretion of saliva which begins about two days after the division and persists for a period of about two or three weeks. At the end of this time the gland is much smaller than the one on the opposite side and exhibits a characteristic picture of degeneration.¹ The cells are small and their nuclei irregular, fragmented and deeply colored. These changes may be rendered more conspicuous by the simultaneous division of the sympathetic fibers. Obviously, we are dealing here with a trophic disturbance in this gland which finally leads to its exhaustion. In other words, in the absence of its normal innervation, the local nervous elements are quite unable to effect an anabolism sufficient to compensate for the catabolism resulting in consequence of some endogenous stimulus. The processes of dissimulation finally gain the upper hand and cease only after the secretory material has been completely exhausted.

The Innervation of the Salivary Glands.—The secretion of saliva is a reflex act made possible by the existence of definite reflex circuits. The center controlling this act is situated in the medulla oblongata, but its boundaries have not been established with any degree of definiteness. It is safe to assume, however, that a part of it is formed by the deep origins of those nerves which participate in the innervation of the salivary glands, namely by the nuclei of the facial and glossopharyngeal nerves. Salivation is a function apportioned to the autonomic system. In last analysis, therefore, the peripheral nerves controlling this process are autonomic in their character, although they select typical cerebrospinal paths in gaining access to the center.

On the *efferent or motor side*, the salivary center is connected with the different glands by means of two separate sets of fibers, constituting the so-called cerebral and sympathetic paths. The former reach the glands by way of one or the other of the cranial nerves, while the latter first enter the thoracic sympathetic system and then ascend in the cervical sympathetic nerve. Having attained the superior cervical ganglion, they follow in the course of the different arteries to their respective glands.

This arrangement may be studied most conveniently in the dog, in which animal the cerebral nerve supply of the parotid is derived

¹ Maximow, *Archiv für mikr. Anat.*, lviii, 1901, 1, and Gerhardt and Burton-Opitz, *Pflüger's Archiv*, xcvi, 1903, 317.

from the system of the glossopharyngeal nerve, and that of the submaxillary from the system of the facial nerve. In the first instance, these fibers become recognizable in the tympanic branch of the glossopharyngeus which is known as the nerve of Jacobson. From here

FIG. 491.—SCHEMATIC REPRESENTATION OF THE COURSE OF THE CEREBRAL FIBERS TO THE PAROTID GLAND. (Howell.)

they reach the otic ganglion by way of the small superficial petrosal nerve. Upon their emergence from this autonomic outpost, they attain the parotid gland by following the highway of the auriculo-

FIG. 492.—SCHEMATIC REPRESENTATION OF THE COURSE OF THE CHORDA TYMPANI NERVE TO THE SUBMAXILLARY GLAND. (Howell.)

temporal branch of the inferior maxillary division of the fifth cranial nerve (Fig. 491). The cerebral fibers of the submaxillary gland leave the facial system in the form of a small nerve, known as the chorda tympani. After their emergence from the tympanic cavity through

the Glaserian fissure, they attach themselves to the lingual branch of the fifth cranial nerve. Having followed this highway for a short distance, they again pursue a separate course along Wharton's duct to the hilum of this gland. A small ganglion, known as the submaxillary ganglion, marks the point where these fibers diverge from the lingual nerve (Fig. 492). Langley, however, believes that the fibers destined for the submaxillary gland do not form synapses here, but merely skirt its border, while those fibers which innervate the sublingual gland actually terminate in this structure to be continued as secondary fibers. This ganglion, therefore, should really be called the sublingual ganglion.

Those fibers, which first enter the sympathetic system, traverse the thoracic ganglia and become a part of the cervical sympathetic nerve. They form synapses in the superior cervical ganglion, whence their postganglionic fibers continue onward along the arteries supplying the different salivary glands.

On the *afferent or sensory side*, the salivary center is connected with a number of external as well as internal receptors. Under ordinary conditions, however, the former are of greater value, because a flow of saliva may be evoked by impressions received from the retina and olfactory cells as well as by stimuli produced by the food as it traverses the oral cavity. Thus, it is a matter of common experience that a flow of saliva may be elicited by the mere smell and sight of food as well as by psychic stimuli. The opposite effect, in the form of a dry mouth and parched throat, is incited by fear, embarrassment and anxiety. Consequently, the salivary center must be connected reflexly with the olfactory cells, the retina and some of the higher association centers. Lastly, this center must be in reflex communication with various general interoceptors, because the feeling of nausea, visceral pain, and other internal sensations frequently give rise to a copious flow of saliva.

The Mechanism of Salivary Secretion.—The secretion of saliva is a reflex act which may be evoked by the stimulation of any one of the receptors just mentioned. It should not be assumed, however, that these stimulations affect the different glands in a perfectly uniform manner, giving rise to a definite quality of saliva under all circumstances. The truth seems to be that the quality of the secretion varies with the quality of the stimulation. Thus, a more specific excitation of the parotid yields a serous saliva, and a more specific stimulation of the sublingual a mucous saliva. Such variations are not at all uncommon, and their occurrence may easily be demonstrated experimentally. Thus, if a fistulous communication is established between the duct of the submaxillary gland and the outside, a copious flow of saliva may be produced by the introduction into the mouth of either a 0.25 per cent. solution of hydrochloric acid or of powdered meat. On analysis it will then be found that the type of saliva secreted after the ingestion of meat, contains approximately twice as much solid ma-

terial as that obtained with the aid of the acid. What is true of the submaxillary must also be true of the other glands; but naturally, these differences cannot be detected so readily directly within the mouth, because all three secretions are poured into this common reservoir at one time. It is also of interest to note that the daily amount of saliva furnished by each gland exceeds its weight ten or twelve times. The total production of these glands, therefore, cannot be less than one liter, this quantity including the small portion which is poured forth constantly to moisten the surfaces of the mouth as well as those extra amounts which are produced from time to time in response to stimulations.

The facts which may be mentioned in explanation of these fundamental differences in the saliva, must necessarily be of a very general kind, because they are based upon the still very obscure microphysical and microchemical occurrences in cells. Thus, it may be assumed that the nerves innervating the salivary glands are capable of conveying impulses of different kinds or that each nerve contains separate sets of fibers which react specifically to different stimuli.¹ This assumption finds substantiation in the fact that the action of the cerebral (parasympathetic) nerve is quite different from that of the sympathetic nerve. To illustrate, if the chorda tympani is stimulated, it will be found that the submaxillary gland reddens and becomes warmer to the touch, because its blood-vessels are markedly dilated.² It may then also be observed that the blood returned from this gland possesses a much brighter color, and that the small vein draining it pulsates markedly. These pulsations are due to the arterial pulse which is propagated at this time directly through the dilated and non-resistant capillaries. Contrariwise, the excitation of the cervical sympathetic nerve causes this gland to become pale, to decrease in volume, and to become distinctly cooler to the touch. These changes unmistakably point to alterations in its blood-supply, the excitation of the chorda tympani giving rise to vaso-dilatation and the stimulation of the sympathetic fibers to vaso-constriction.³

Curiously enough, these changes in the vascularity of this gland are associated with very decided changes in the quantity and quality of the saliva.⁴ Very soon after the beginning of the stimulation of the chorda tympani, Wharton's duct becomes highly distended and discharges a quantity of saliva four or five times larger than normal. The secretion itself is very watery and possesses only a slight viscosity. It contains no more than 1 or 2 per cent. of total solids. If a sufficiently long interval is allowed to separate the successive stimulations,

¹ Pawlow, *Ergebn. der Physiol.*, iii, 1905.

² Cl. Bernard, *Compt. rend.*, 1858.

³ These differences may also be recognized by means of the stromuhr or current measurer. See: Burton-Opitz, *Jour. of Physiol.*, xxx, 1903, 132.

⁴ First observed by Ludwig, *Arbeiten aus dem physiol. Institut zu Leipzig*, 1851.

this experiment may be repeated for many hours without any apparent decrease in the intensity of the reaction. Contrary to this result, the excitation of the cervical sympathetic nerve yields only a few drops of saliva which is characterized by its turbidity and richness in total solids (6 per cent.). On the one hand, therefore, we obtain a vasodilatation and copious flow of a very watery saliva and, on the other, a vaso-constriction and a scanty flow of a very viscous saliva. Very similar changes may be evoked in the parotid gland; in this case, however, the excitation of the sympathetic nerve does not yield an appreciable quantity of secretion, although it produces marked histological changes in the secretory cells.

Regarding the intracellular changes little can be said unless we confine this discussion to the structural alterations during rest and activity. Secretion is essentially a transudation of water from the blood-vessels into the excretory ducts, controlled, of course, by the constituents of the cell. It is conceivable that the agents most actively concerned in this process are those granules of the cytoplasm which take up water, swell and discharge their contents into the ducts. How this osmotic play may be influenced by impulses brought to these cells by way of the secretory fibers, is largely a matter of speculation into which we cannot enter at this time. It is certain, however, that the cell is not merely a pumping mechanism for the flow of water, but also serves as a generator of organic material which is later on transferred into the watery medium.¹ Obviously, the waves of excitation derived from the chorda tympani, must increase this transudation as well as rupture the granules, but it is also conceivable that the aforesaid secretory nerves may innervate different elements of the gland. While it has been shown that they terminate around the various alveoli, forming here delicate arborizations below the basement membrane, certain evidence has also been presented to prove that the cerebral autonomic fibers are apportioned to the chief cells and the sympathetic fibers to the cells of the crescents of Gianuzzi. At least, this arrangement seems to prevail in the submaxillary gland of the dog. Upon the basis of Müller's Law of the specific nerve energy we might then assume that these mechanisms react differently to different kinds of stimulations enacted by the food. In one case, we would obtain a typical chorda-saliva, and in another, a typical sympathetic-saliva, or even a mixture of the two.

Barcroft and Piper² have sought to obtain a measure of the energy evolved by a secreting gland by ascertaining its respiratory exchange when resting and when active. Thus, it has been found that the submaxillary gland of the dog consumes 0.25 c.c. of oxygen in a minute and liberates 0.17 c.c. of carbon dioxide. During this time 6 grams of gland-tissue furnish about 1.1 calorie of heat. The active organ, on

¹ Macallum introduces the factor of differences in surface-tension, *Ergebn. der Physiol.*, xi, 1911.

² *Jour. of Physiol.*, xlv, 1912, 359.

the other hand, requires 0.86 c.c. of oxygen per minute and yields 6.39 c.c. of carbon dioxide.

It has also been noted that the activity of the salivary glands is accompanied by changes in their electrical potential which originate in the formation of electrolytes and their movements through animal membranes. These differences are similar to those observed in active muscle and nerve, and may be detected by applying the poles of a galvanometer to the surface and the hilum of the gland. The surface is then galvanometrically positive. In the case of the submaxillary gland, the stimulation of the chorda tympani first increases and then decreases this positivity, which fact signifies that this current possesses a diphasic character. The one evoked by the stimulation of the sympathetic nerve, on the other hand, presents itself merely as a negative variation of the current of rest.

The Action of Drugs upon the Secretion of Saliva.—If *atropin* is administered intravenously or is injected into the duct of the submaxillary gland, the stimulation of the chorda tympani soon ceases to produce its characteristic secretory effect. Meanwhile, however, the excitation of the sympathetic nerve remains effective and much larger doses of this alkaloid are required to abolish the flow of this type of saliva. The vaso-dilator action of the chorda also persists until additional doses have been administered. This peculiar result suggests that atropin paralyzes the endings of the cerebral autonomic fibers, but does not affect the secreting cells themselves. Secondly, it points toward a definite chemical difference between the nervous elements constituting the cerebral or parasympathetic system and those forming the sympathetic system proper. *Pilocarpin* evokes a copious flow of saliva which is accompanied by vaso-dilatation. This agent, therefore, possesses an antagonistic action to the preceding one and stimulates the endings of the cerebral nerve. *Ergotoxin* paralyzes the sympathetic mechanism, but does not affect the one controlled by the chorda tympani. This fact, again, speaks for the previous contention that the cerebral and sympathetic autonomic fibers differ from one another in their chemical constitution. *Adrenalin* evokes a constriction of the blood-vessels which, in some animals, is soon followed by a vaso-dilatation and a considerable flow of saliva.

Nicotin may be used to abolish the action of the secretory nerves, but since it does not affect the secreting cells nor the nerve terminals, it must produce this effect in an indirect way. It is a well-known fact that it destroys the synapses and hence, may be employed to cause a functional discontinuity between the preganglionic and postganglionic paths. Thus, if the submaxillary (sublingual) ganglion is moistened with a solution of this alkaloid, the stimulation of the chorda tympani centrally to this ganglion ceases to evoke a secretion from the sublingual gland, because the fibers destined for this organ are relayed at this point.¹ Moreover, inasmuch as this procedure does not block

¹ Langley, Proc. R. Soc., London, 1889.

the impulses apportioned to the submaxillary gland it may rightly be concluded that the fibers innervating this organ pass directly through the aforesaid ganglion without forming new connections.

Facts Disproving the Filtration Theory.—While it cannot be denied that filtration plays an important part in the secretion of saliva, we are not warranted in believing that it is the only factor mediating this process. It has previously been noted that the excitation of the chorda tympani gives rise to a vaso-dilatation and a copious flow of a very watery type of saliva, while the stimulation of the cervical sympathetic nerve evokes a vaso-constriction and a scanty flow of a very viscous saliva. While these changes may at first be thought to favor filtration, they cannot be interpreted in this way if contrasted with such facts as the following:

(a) We have noted above that the formation of saliva is not wholly dependent upon the blood-supply, but is more closely related to the influences of the nervous system.

(b) It has also been pointed out that this secretion may be either increased or decreased by drugs without altering the pressure existing in the capillaries of the gland from which the material is taken.¹

(c) Inasmuch as the saliva contains bodies, such as mucin and ptyalin, which are not present in the body-fluids, the secreting cells must possess the specific power of forming them. Carlson states that saliva also contains a diastase which is present here in smaller amounts than in the blood.

(d) It has been shown that saliva may also be secreted by the submaxillary glands after its artery has been ligated, and that

(e) The normal gland may be made to secrete against a higher pressure than the capillary pressure.

Under ordinary conditions, the salivary cells derive their secretory material from the blood-capillaries in which the pressure does not rise above 40 to 60 mm. Hg. They then discharge it into the salivary duct in which the pressure approximates zero. This arrangement favors filtration. It can be shown, however, that these cells are also able to secrete against a pressure which not only exceeds the capillary pressure, but also that prevailing in the carotid artery. Thus, if Wharton's duct is connected with a mercury manometer, and the chorda tympani is stimulated repeatedly at intervals, it will be found that the mercury continues to rise until it eventually indicates a pressure at least twice as high as that existing in the capillaries of the submaxillary gland. In fact, Hill and Flack² have succeeded in obtaining a salivary pressure of 240 mm. Hg against a blood-pressure of 130 mm. Hg. Now, if filtration were the only factor concerned in the formation of saliva, a relationship of this kind could not be successfully established. The same conclusion may be derived from the fact that even the

¹ Sarmus, *Zeitschr. für Biologie*, lviii, 1912, 185.

² *Proc. R. Soc. London*, lxxxv, 1912.

bloodless gland is able to secrete saliva, but since this organ is unable to acquire new material, the secretion will be scanty in amount.

The General Character of Saliva.—When collected directly from the mouth, saliva is a transparent, slightly opalescent and slimy liquid, possessing a moderate viscosity and a specific gravity of 1.002 to 1.006.¹ On standing it becomes cloudy, this change being due to the deposition of calcium carbonate in consequence of the escape of carbonic acid which formerly retained this salt in the form of its bicarbonate. The reaction of saliva is slightly alkaline, but may become moderately sour during the night and during fevers and digestive disorders. The reason for this is the diminution in its quantity which favors the bacterial decomposition of its organic constituents. Its active principle, ptyalin, ceases to act in a markedly alkaline or slightly acid medium; in fact, free hydrochloric acid in an amount equalling a 0.003 per cent. solution suffices to stop its action entirely. Temperatures of 0° C. and 65° to 70° C. have a similar effect.

The quantity of saliva secreted in a day has been estimated in man at 1 to 2 liters, in horses at 40 liters, and in the large ruminating animals at 60 liters. It contains 0.5 per cent. of solids, which may be classified as follows:

Organic: Mucin, which gives to it its ropy, mucilaginous character.

Ptyalin, an amylolytic enzyme.

Protein, of the nature of a globulin.

Potassium sulphocyanide.

Inorganic: Sodium chlorid, sodium carbonate.

Calcium phosphate and carbonate, magnesium phosphate and potassium chlorid.

Suspended in the saliva are desquamated epithelial cells, disintegrating leukocytes, the so-called "salivary corpuscles," gland cells and clumps of mucin. Among the living organisms might be mentioned a number of saprophytes, such as *leptothrix buccalis*, and pathogenic bacteria.

CHAPTER LXXIX

THE DIGESTIVE SECRETIONS (CONTINUED)

B. THE GASTRIC AND PANCREATIC SECRETIONS

The Gastric Glands.—The cavity of the stomach is divided into a cardiac, fundic and pyloric portion. It is lined throughout by a soft and thick mucosa which presents a honeycomb appearance owing to the presence of numerous shallow polygonal depressions. Its unusual thickness is due very largely to the fact that it is made up of an almost infinite number of closely packed, long tubular glands which are held

¹ Burton-Opitz, *Biochem. Bull.*, 1919; Neilson and Terry, *Am. Jour. of Physiol.*, xv, 1906, 406; Tezaš, *Maly*, xxv, 1905.

together by slight amounts of reticular tissue. In between these glands are found columnar goblet cells which secrete mucus. The former consist of a basement membrane which is covered externally with epithelium. Toward the gastric surface the enlarged outer portions of these tubules narrow into a duct which is lined by short columnar cells. In many cases the latter are mucus-secreting, the same as those situated directly upon the inner surface of the mucosa. The epithelium of the outer portions of these tubules differs somewhat

FIG. 493.

FIG. 493.—DIAGRAMMATIC REPRESENTATION OF A FUNDIC GLAND.

C, Chief cells; P, parietal cells; D, duct of gland; N, neck of gland.

FIG. 494.

FIG. 494.—PART OF TUBULE OF A FUNDUS GLAND, WITH THE LUMEN AND SECRETORY CANALICULI STAINED BLACK; THE GLAND-CELLS ARE ALSO SHOWN.

C, Chief or central cells; p, parietal or oxyntic cells; l, lumen of tubule prolonged into arborescent canaliculi which penetrate to the parietal cells. (Zimmermann.)

in different parts of the stomach, so that we are able to recognize three distinct types of gastric glands, namely:

(a) The *glands of the cardiac end*, which are simple tubular or tubulo-racemose in character and are lined by short columnar cells containing much granular material. They are few in number and are found principally in the immediate vicinity of the esophageal-gastric junction.

(b) The *glands of the fundus*, which are distributed throughout the remaining portion of the cardia and the entire fundus. They consist as a rule of three or four long tubular glands which unite into a short duct. The low columnar cells lining these ducts gradually pass over into the true secretory cells which are somewhat polyhedral in shape and are partly filled with granules occupying a posi-

tion next to the lumen of the duct. These cells line the entire secretory portion of these glands and are known as *central or chief cells*. Wedged in between these and the basement membrane are a number of isolated cells which present a spheroidal or ovoid shape, and are connected with the main duct by a network of minute channels situated in between the chief cells. Nearer the duct, these cells are more abundant and occupy a position in between the chief cells and close to the lumen (Bensley). These cells are known as the *parietal or oxyntic (acid) cells*.

(c) The *glands of the pyloric end*, which are scattered throughout the pyloric canal, are much longer than those of the fundus and are made up wholly of chief cells. The latter bear a close resemblance to those composing the fundic glands, but are not quite so granular. Directly at the pylorus they increase in size, and become more convoluted and more deeply seated. They are thus gradually transformed into the glands of Brunner of the submucous layer of the duodenum.

Histological Changes in the Gastric Glands on Secretion.—According to Heidenhain, the chief cells of the inactive glands are large and clear, save for a certain amount of granular material which is collected very largely near the duct. During secretion, these granules are discharged into the duct, leaving the outer zones of the cells perfectly clear.¹ The parietal cells undergo a similar diminution in their size, but do not exhibit so distinct a clearing of their cytoplasm. Thus, we are again confronted by the fact that these cells do not merely form a pumping mechanism for water, but actively concentrate the original liquid by preformed material.

The Origin of the Active Principles of Gastric Juice.—Heidenhain² conceived the idea of isolating a certain portion of the stomach and giving it an artificial fistulous opening to the outside through which gastric juice could be obtained separately from its different segments. This operative procedure has been improved upon by Pawlow³ in such a way that these gastric pockets need not be deprived of their normal blood and nerve supply. Upon analysis of these different samples of gastric juice it was found that the secretion from the pyloric end is free from hydrochloric acid, but not from pepsin, while that from a cul-de-sac of the fundus is strongly acid in reaction and contains much pepsin. Inasmuch as the pyloric glands are made up of chief cells, while the fundic glands also embrace border cells, it was then concluded that the pepsin is furnished by the chief cells, and the hydrochloric acid by the parietal cells.

In support of this hypothesis it has been shown that the esophagus of the frog is beset with glands which are made up of chief cells and secrete only pepsin, while the glands of the fundus of the stomach are composed of ovoidal cells which produce large quantities of acid but little pepsin. Further light is thrown upon this topic by the fact that the secretion taken from the pyloric cul-de-sac, does not digest protein material nor curdle milk unless it is acidified by the addition of dilute hydrochloric acid. Thus, while these glands secrete pepsin, this agent remains impotent as long as it is permitted to remain in an

¹ Langley, Jour. of Physiol. iii, 1880, 269.

² Hermann's Handb. der Physiol., 1883.

³ Die Arbeit der Verdauungsdrüsen, Wiesbaden, 1898.

alkaline medium. Curiously enough, therefore, we are confronted here by the peculiar functional arrangement that the alkaline product of the chief cells is acidified almost immediately by the secretion of the parietal cells, and that the alkaline juice of the pyloric part of the stomach must first be mixed with the fundic acid before it can exert its characteristic action.

The genesis of hydrochloric acid has also received attention from the chemists. Thus, it has been suggested that it is derived from the chlorids of the blood, but the nature of this decomposition is not known. The contrary view is that it originates from the sodium chlorid of the food upon the surface of the gastric mucosa. The latter view, however, could be criticized upon the ground that a copious secretion of gastric juice containing an abundant quantity of hydrochloric acid, may also be evoked without the introduction of food into the stomach; for example, by the process of sham-feeding, or by allowing an animal to see or to smell food. More recently, the preceding hypothesis pertaining to the origin of the hydrochloric acid in the parietal cells has received additional support in the results of the microchemical tests of Fitzgerald¹ and Hammett.² On injecting a ferrocyanid and a ferric salt into the circulation of animals, a deposition of Prussian blue was noted not only in the lumina of the gastric glands but also in the canaliculi of the parietal cells and even within the cytoplasm of the latter. Since this characteristic precipitate was not found in the chief cells and results only in the presence of free acid, it was concluded that the hydrochloric acid originates in the border cells. Harvey and Bensley³ are at issue with this view, because they state that the parietal cells are alkaline in their reaction and believe that a deposition of this coloring material takes place only upon the mucosa of the stomach and in the orifices of the ducts of the different glands. Without entering in detail into the technique of the microchemical tests of Hammett, it may be stated that these later experiments fully confirm the contention of Heidenhain that the parietal cells secrete the hydrochloric acid.

The gastric glands, therefore, present the same functional picture as the salivary glands. They are not merely passive filters but living laboratories in which the contents of the blood and lymph are drawn upon to yield new and very characteristic vital products. This can easily be proven by comparing the composition of the gastric secretion with that of the body-fluids. Thus, we obtain in the former such characteristic bodies as mucin, pepsin, hydrochloric acid, and rennin.

Methods Employed to Obtain Gastric Juice.—The experiments of the older observers (Spallanzani, 1729–1799) were carried out with various foods which were sewed in linen bags or enclosed in perforated capsules of wood. Clean sponges attached to strings have also been used, the sponges being removed later on and their contents squeezed

¹ Proc. R. Soc., London, 1910.

² Anat. Record, ix, 1915, 21.

³ Biolog. Bull., xxiii, 1912, 225.

out. These procedures have been displaced in more recent years by the method of aspirating or siphoning the gastric juice by means of a long tube of rubber inserted through the esophagus. A number of cases have also been reported in recent years of persons in whom it became necessary to establish a free communication between the gastric cavity and the outside. The first of these has been recorded by the American frontier physician Beaumont,¹ the subject being the Canadian hunter Alexis St. Martin, whose abdominal and gastric walls had been extensively lacerated by the premature discharge of a gun, so that even the lung protruded from the wound. In healing, a fistulous communication was formed between the outside and the cavity of the stomach, but the escape of the gastric contents was prevented by a flap of mucous membrane which acted as a valve and did not allow of an unobstructed view of the interior of this organ. Beaumont determined the time it took to digest meals and found that pork required a longer period for its digestion than beef. He also noted the character of the gastric mucosa in health and disease, and obtained sufficient quantities of pure gastric juice for analysis. The results of these studies are accepted even to-day as wholly accurate. Furthermore, he introduced various foods through this fistulous opening and withdrew them again later on to see what changes had taken place in them.

Since the time of Beaumont gastric fistulas have been established in a number of persons suffering from occlusion of the esophagus in consequence of erosion by corrosive alkali. Cases of this kind have been reported by Richet, Sommerfeld and Roder,² Bickel,³ Umber,⁴ Kaznelson,⁵ and Carlson.⁶ The subject of the most recent report was operated upon 16 years ago and has since led a normal life, offering himself repeatedly for physiological observation. This same condition may be produced in animals by operative means, the fistulous opening in the abdominal wall being permanently closed by a silver cannula. The outside cover of the latter is made so that it can be removed at any time for the purpose of procuring gastric juice. In this category also belong the procedures of Heidenhain and Pawlow which permit of the resection and isolation of a particular portion of the stomach and the separate study of its secretion.

Artificial gastric juice may be prepared by extracting macerated gastric mucosa with dilute hydrochloric acid. This liquid is filtered and warmed to the temperature of the body whenever required for use. For coagulated albumin it should have a strength of 0.16 per cent. Pepsin may be obtained by placing the washed mucosa in alcohol

¹ The Physiology of Digestion, 1833.

² Archiv für Physiol., 1905.

³ Deutsch. med. Wochenschr., 1906.

⁴ Berliner klin Wochenschr., 1905.

⁵ Pflüger's Archiv, xcvi, 1907, 327.

⁶ Am. Jour. of Physiol., xxxi, 1912, 151.

for 24 hours, drying it, pulverizing it and extracting it in glycerin for 6 or 7 days. On addition of alcohol to the filtrate, the pepsin is precipitated, which may then be added to dilute hydrochloric acid.

The Characteristics of Gastric Juice.—When obtained from a fasting animal, gastric juice is quite clear, odorless, acid in reaction, and sour to the taste. Its specific gravity varies between 1.002 and 1.006 and its depression of the freezing point between 0.47° and 0.65° C.¹ Its quantity may be considerable, large dogs yielding as much as 1 liter in the course of 3 hours. Human subjects secrete 700 c.c. during a moderate meal and an average total per day of 1500 c.c. As Carlson² has pointed out, the gastric glands of a healthy person are never wholly dormant, but secrete continuously in amounts varying between 2 and 50 c.c. in an hour; the higher figures, however, are exceptional. Gastric juice contains only 0.3 to 0.6 per cent. of total solids, as follows:

Acid.	0.46–0.58 per cent.
Chlorin.	0.49–0.62 per cent.
Total solids.	0.43–0.60 per cent.
Ash	0.06–0.16 per cent.

If gastric juice is cooled and is allowed to stand, it becomes cloudy and gives rise to a deposit of finely granular and highly refracting material which appears to consist of the active principle pepsin. This agent unfolds its action only in an acid medium which is supplied to it by the *hydrochloric acid* (Prout, 1824). Since the latter is present in amounts varying, in dogs, between 0.45 and 0.58 per cent. and, in man, between 0.25 and 0.35 per cent., about 3 grams of hydrochloric acid must be produced at each meal. In some persons, however, there may be an achlorhydria or absence of hydrochloric acid, although some peptic digestion may still be present. A condition of this kind constitutes a diagnostic sign of considerable value. It commonly develops in the course of carcinoma of the stomach. The reverse condition is hyperchlorhydria, which is usually associated with a hyperpeptic activity and a deficiency in mucus. The cause of this excess in acid usually lies in a hyperirritability of the nervous system, as well as in lesions producing a constant stimulation of the gastric mucosa, such as ulcers and growths elsewhere in the abdominal cavity.

The acidity of the gastric juice is usually ascertained by means of a test breakfast. When only a light evening meal is taken, the stomach should be empty in the morning, *i.e.*, after a period of rest of about 12 hours. The breakfast should consist of a roll or five crackers or biscuits and a cup of weak tea. A sample of gastric juice is obtained 45 minutes later by means of the stomach tube. While the analytical procedures to be followed in this case cannot be described in detail in a book of this kind, it might be mentioned that the unfiltered juice may be titrated with N/10 NaOH, using phenolphthalein as an indicator. Although the determination of the free hydrochloric acid may be made with Günzberg's or Töper's reagent,³ the most accurate procedure is to ascertain the number of hydrogen ions in the juice in accordance with the gas-chain method.⁴ The former reagent con-

¹ Rosemann, Pfüger's Archiv, cxviii, 1907, 467, and Sommerfeld, Archiv für Physiologie, 1905, 455.

² Am. Jour. of Physiol., xxxvii, 1915, 50.

³ Zeitschr. für physiol. Chemie, xix, 1894, 104; also: Christianson, Bioch. Zeitschr., xlvi, 1912, 24.

⁴ Panton and Tidy, Analysis of Gastric Contents, Quart. Jour. of Medicine, iv, 1910–1911.

sists of a mixture of phloroglucin and vanillin dissolved in absolute alcohol, and the latter of dimethylamino-azo-benzene.

The first amount of hydrochloric acid secreted usually gives a negative reaction with these reagents, because it is bound by the albuminous bodies to form acid albuminates. Furthermore, while pure gastric juice contains no lactic acid, this acid is always present in the gastric contents composed of the pure juice and a mixture of partly digested food. It arises in consequence of the fermentation of carbohydrates which are attacked by the bacillus lactici ingested with the food, and are converted into sugar and lactic acid. Under ordinary conditions, however, the action of this bacillus is cut short by the hydrochloric acid, because even an acidity of only 0.07 to 0.08 per cent. HCl absolutely prevents the formation of lactic acid from dextrose. Consequently, lactic acid must be formed chiefly during the early stages of gastric digestion or when there is a deficiency in hydrochloric acid, as during carcinomatous affections of the stomach. But naturally, the acidity of normal gastric juice is not due to lactic acid, as may be proved by taking this acid up with ether and applying Uffelmann's test¹ to the extract.

Pepsin (Th. Schwann, 1836) is not present in the cells of the gastric glands as such, but in its inactive form, known as stored pepsin or pepsinogen.¹ The latter, therefore, may be regarded as the precursor or mother-substance of this ferment which assumes its active condition only after its escape from the cells and in the presence of hydrochloric acid. This is proved by the fact that the mucous membrane of the dog or pig, which is alkaline or neutral in reaction, may be extracted with water and mixed with hydrochloric or some other acid (0.3 per cent.) to form a powerful digestive medium. Contrariwise, gastric mucosa extracted under glycerin may be kept for some time without any indication of self-digestion or autolysis. This process, however, sets in immediately if an acid is added to this extract. Furthermore, Langley² has shown that pepsin is very sensitive to alkalies, because when neutralized with sodium hydrate and again acidified, it loses much of its former potency. An extract of the mucosa, however, may be made slightly alkaline for a short time without losing its activity on acidification, while an acid extract cannot be made alkaline without permanently destroying its power. Another means of showing that the substance contained in the gastric cells is different from actual pepsin, is furnished by the fact that carbonic anhydrid gas destroys the action of the pepsinogen contained in a neutral aqueous extract of frog's esophagus. Contrariwise, if this extract is first acidified and then neutralized, the passage of carbonic anhydrid through it does not nullify its power.

Pepsin is a colloidal substance. As such it is not dialyzed through animal membranes or parchment paper. Regarding its chemical nature we know very little. Pikelharing³ and Nencki and Lieber⁴ classify it as a protein or protein-like body of the elementary composition: C, 51.26 per cent., H, 6.74 per cent., N, 14.33 per cent., and S, 1.5 per cent. It should be remembered, however, that this ferment varies in its composition in different animals, because it presents not only certain differences in the optimum concentration of the acid required to activate it, but also in its resistance to heat. The question of what becomes of the pepsin after it has unfolded its ferment-action, cannot be answered with certainty. The probability is that the largest amount of it is destroyed in the intestine by the other enzymes or by the bacteria, but a small portion of it may also be absorbed and enter the blood and urine.

Rennin.—The gastric juice of mammals, as well as aqueous infusions of the gastric mucosa, possesses the property of curdling milk. This process is essentially a coagulation during which a soluble protein contained in milk is converted into its

¹ Hammarsten, Zeitschr. für Physiol. Chemie, xcii, 1914, 121.

² Jour. of Physiol., vii, 1886, 371.

³ Zeitschr. für physiol. Chemie, xxxv, 1902, 8.

⁴ Ibid., xxxii, 1901, 261.

insoluble form. The active agent concerned in this change is an enzyme, known as rennin, rennet or chymosin. Like pepsin, this substance is produced by the chief cells, being stored in them in its inactive form as prorennin or, prochymosin. When passed into the ducts, it assumes its characteristic action of clotting milk, but only in the presence of calcium and hydrochloric acid. Chemically, this process consists in a conversion of the soluble caseinogen of milk into the insoluble casein. Together with the other proteins, the latter is then subjected to the proteolytic action of the pepsin.

Rennin, however, is not the only milk-clotting enzyme. Similar bodies are present in the pancreatic juice, the intestinal juice, the juices of certain fruits, such as the cocoanut and the pineapple, and in many bacteria. In fact, since the curdling of milk is a common phenomenon of proteolytic processes anywhere in nature, some authors believe that it is not caused by a specific enzyme but by the proteolytic ferment itself. Opposed to this view is the less probable one that a special non-proteolytic coagulating substance is almost universally present in nature.

This controversy brings up the question pertaining to the possible identity of rennin and pepsin, which must still be considered as not definitely settled. To be sure, Hammarsten has shown that pepsin in its pure form possesses coagulating properties, but certain facts are also at hand to prove that rennin and pepsin are very unlike one another.¹ If it is assumed that the clotting of milk is a general property of all proteolytic enzymes, the stomach must contain two such agents, namely pepsin and rennin. The former is a product of the fundic glands and is activated only in an acid medium. The latter, on the other hand, is chiefly a product of the pyloric glands and acts in an acid as well as in a neutral medium. In this regard, therefore, it is more like the trypsin of the pancreatic juice and the erepsin of the intestinal secretion. As is usual with many biological properties, these enzymes are unequally distributed in different animals and undergo changes in their potency even in the same animal. Thus, we find that rennin is especially abundant in the stomachs of suckling animals, and that its amount or potency gradually diminishes in later years and particularly in the carnivora. Its place is then taken by the pepsin which acts in an acid medium at a time when the adult stomach has acquired a much greater resistance than it possesses shortly after birth.

In addition, gastric juice contains a fat-splitting ferment or lipase which possesses the property of splitting emulsified neutral fats into glycerin and fatty acids.² Such fats are present in milk. The non-emulsified fat, on the other hand, it allows to traverse the stomach practically unchanged. This lipase exists in the mucosa in the form of a mother-substance. The fact that it is of much greater importance in the suckling than in the adult is in accordance with the character of the food of the young, which consists largely of emulsified fat.

The Resistance of the Stomach to the Gastric Ferments.—Since the proteolytic ferment pepsin acts in an acid medium, it may seem strange that the gastric wall is normally exempt from its digestive power, while a stomach which has been rendered abnormal by interfering with its blood-supply, rapidly undergoes autolytic changes. This is also true of the excised organ when immersed in its own juice. A number of theories have been advanced in explanation of these facts, all of which embody the belief that the lining cells of the stomach are normally resistant against the gastric juice. Thus, it has been stated that the surface of the stomach is always covered with a layer of

¹ Schmidt-Nielsen, *Zeitschr. für physiol. Chemie*, xlviii, 1906, 92; Fuld, *Ergebn. der Physiol.*, i, 1902; and Pawlow and Pavutschuk, *Zeitschr. für physik. Chemie*, xlii, 1904, 415.

² Volhard, *Zeitschr. für klin. Med.*, xlii, 1900, 414.

mucus which acts as a protection for the underlying cells. In practically all cases of hyperchlorhydria, however, the secretion of mucus is greatly diminished, without thus creating an especially favorable condition for the formation of ulcers. Contrariwise, mucus may be secreted in excessive amounts in the presence of formidable ulcers. Another theory holds that the aforesaid resistance of the gastric wall is due to the alkalinity of its constituent cells which tends to neutralize the gastric juice anointing them. Going a step farther in this direction, we might say that the cause of the resistance of the gastric mucosa against digestion lies in the normality of its life processes. The latter consist in oxidations, and hence, it is evident that the pepsin immediately exposed to them must be rendered inert by being oxidized. In this connection it is of interest to note that the cells of the gastric mucosa possess an intense power of oxidation. This observation of Lillie¹ is in accord with that of Burge,² proving that pepsin is easily destroyed by oxidation. Under normal conditions, therefore, a balance is established between the intracellular oxidations and the digestive action of the neighboring pepsin. Whenever this balance is destroyed, the cells are digested with the formation of erosions of varying size.

These oxidative processes may be disturbed in different ways; for example, by cutting off the blood supply of a particular area of the stomach or by depressing the circulatory efficiency of the animal as a whole. Thus, a local anemia may be established in consequence of tumors, wounds, stricture of the pylorus and thrombosis; and a general circulatory deficiency in consequence of hemorrhage, anemia, poisons and toxins.

The Regulation of the Secretion of Gastric Juice by Hormones and Vitamines.—In general, it may be said that glands may be made to secrete in two ways, namely, indirectly by means of chemical agents contained in the blood, and directly by the stimulation of the nerve fibers innervating the different cells. Eventually, of course, both types of stimuli are conveyed to the cells, exciting their cytoplasm at first hand. Agents which possess this stimulating action, most generally arise elsewhere in the body and are brought to the gland in the bloodstream. Thus, it has been found that the pituitary body gives rise to an internal secretion which increases the flow of milk from the mammary gland, and that the lining of the duodenum produces an agent which initiates the flow of pancreatic juice. As far as the stomach is concerned, Edkins³ has shown that the injection into the bloodstream of broth, dextrin, peptone or acid does not augment the flow of gastric juice, while an extract of the mucous membrane of the pylorus invariably acts as a potent secretagogue. It is evident, therefore, that the mucosa of the stomach produces a hormone, known

¹ Am. Jour. of Physiol., vii, 1902, 413.

² Ibid., xxxvii, 1915, 462.

³ Jour. of Physiol., xxxiv, 1906, 133.

as *gastric secretin* or *gastrin*, which is liberated during the process of gastric digestion and serves as a stimulus to the local glands. Secondly, it cannot be doubted that food itself contains certain stimulating substances which upon their absorption exert a definite synthetic or constructive influence upon all cellular processes. These accessory bodies are known as *vitamines*. Practically nothing is known regarding their chemical nature,¹ but we divide them as a rule into two groups, viz.: those soluble in fat which are abundant in butter,² and those soluble in water and alcohol which are present in wheat, maize, cabbage, and in many foods of animal origin.

It must seem strange that an animal fed upon a mixture of pure proteins, fats, carbohydrates, salts and water, will not thrive, but ceases to develop and presently exhibits a complex of symptoms indicative of malnutrition. But if this artificial diet is augmented by some natural food, such as vegetables or milk, the animal immediately begins to develop normally. Hopkins³ divided a large number of young rats into two groups, one of which received a diet of caseinogen, fats, carbohydrates and salts, and the other the same food plus a small ration of fresh milk. Although the consumption of material was practically the same in both groups of animals, the former soon ceased growing, while the latter developed normally. Even man may suffer from these "deficiency-diseases," chief among which are scurvy, beri-beri, pellagra and rickets. Scurvy, for example, used to be prevalent upon sailing vessels when fresh meat, vegetables and fruits were unobtainable, and when fish formed the almost constant diet. As a means of preventing this disease, lime or lemon juice was generally given, it being believed that citric acid and traces of malic acid are essential constituents of food. Scurvy may also develop in infants fed exclusively on pasteurized milk. All the alarming symptoms of this disease may be made to disappear in the course of a day or two by the use of fresh milk or by the addition of orange juice and the white of egg to the former.

Very similar disturbances of nutrition may be incited by the exclusive use of polished rice. Thus, it has been noted in Japan that Kak-Ka (beri-beri) has greatly increased since the primitive mill-stones have been displaced by the modern steel-rollers. In Bengal, on the other hand, where the old methods of milling are still in use, this disease is practically unknown, although rice forms one of the chief foods of this country. A similar disease may be evoked in birds by feeding them only polished rice. This puzzling situation has been cleared up in a large measure by Funk,⁴ who has extracted from the polishings, *i.e.*, from the outer coats of the rice kernel, a basic principle which he calls *vitamine*. Furthermore, it has been found that if these polishings, or their alcoholic extract, are added to the rice prepared in the modern way, this food does not produce the aforesaid disease. After its development, the latter may be quickly remedied by the ingestion of unpolished rice or by eating potatoes, fresh vegetables, fruit, milk, meat and eggs. Yeast is said to contain *vitamines* in considerable amounts and it is assumed that the nutritive value of fermented beverages, such as beer, is in large part due to these bodies. Quite similarly, it is assumed that the value of whole-meal bread does not depend upon its extra amount of protein but probably upon its content in *vitamines*.

It must be concluded, therefore, that the different foods taken into the stomach contain certain substances which in themselves cannot be regarded as foods nor as condiments, but which are absolutely

¹ McCollum, Simmonds and Fitz, *Am. Jour. of Physiol.*, lxi, 1916, 361.

² Osborne and Mendel, *Jour. of Biol. Chem.*, xxiv, 1916, 37.

³ *Jour. of Physiol.*, xlv, 1912, 425.

⁴ *Ergebn. der Physiol.*, 1913, 124.

essential for the maintenance of health and growth. While as yet chemically unrecognized, their presence has been proved by physiological means. They play the part of "building stones" in the syntheses of the developing animal. As such, they act upon the secretory processes as well as upon the processes of assimilation and dissimilation. Consequently, they must unfold their function as secretagogues shortly after their entrance into the digestive tract, and must also exert a certain influence upon the activity of the gastric glands. This end they accomplish (a) by stimulating the cells of the gastric glands directly, (b) by entering the blood and influencing the secretory activity of these glands in an indirect way, and (c) by causing a liberation of gastric secretin which in turn affects the glandular elements.

The Nervous Control of the Secretion of Gastric Juice.—Like saliva, gastric juice is secreted continuously, but only in amounts sufficient to lubricate the mucous surfaces. At various times, however, a more copious flow is initiated which finds its origin in stimuli of an occasional character. The latter embrace (a) chemical agents which reach the gastric cells either directly from the cavity of the stomach or indirectly by the blood, and (b) stimuli which act reflexly through particular reflex circuits. It must be evident, however, that these reflex arcs need not be situated in the stomach, at least not their afferent path, or analyzer, because a secretion of gastric juice results not only in consequence of the entrance of food into the stomach, but also upon its being taken into the mouth; in fact, even the mere sight and smell of nutritive substances may serve as an efficient stimulus. The act of chewing, however, does not serve as a stimulant, nor does the intake of an indifferent substance not related to food. Consequently, we may say that the secretion of gastric juice is controlled by nerve impulses of intragastric and extragastric origin produced by palatable substances.

This statement implies that the afferent side of the reflex circuit concerned in gastric secretion is diversified, while the efferent side is not. Relative to the latter, it has been proved that it is contained in the vagus system, because the division of the ventral and dorsal vagi below the origins of their pulmonary and cardiac branches abolishes this reflex, while the stimulation of the distal end of either nerve is followed by a secretion. In addition, it has been stated that these nerves contain musculomotor fibers for the stomach.¹ The splanchnic nerves do not seem to be involved in this secretory reaction, because their division and stimulation remains without effect. We know, however, that these nerves embrace vasomotor fibers for the stomach which traverse the ganglia of the solar plexus and reach this organ by following the highways of the different gastric arteries. Consequently, since their stimulation must lead to a constriction of the gastric blood-vessels, they must limit the quantity of the gastric juice, but in an indirect way and not as secretory nerves. Now, since their action is

¹ Burton-Opitz, Pflüger's Archiv, cxxxv, 1910, 205.

not inhibito-secretory in its nature, they cannot be considered as forming a part of an inhibitor mechanism which acts antagonistically to the vagi nerves. The latter are secretomotors. It seems, therefore, that the vagi nerves are capable of stimulating as well as of inhibiting the flow of the gastric juice, and hence, they must form the chief efferent secretory path between the central nervous system and the stomach.

In considering the effects of the intragastric stimuli, we are confronted by the statement that the mechanical stimulation of the gastric mucosa produces only a discharge of mucus and not of gastric juice. Even water and meat, when introduced through a fistula, give rise to only a slight flow. The same is true of bread and coagulated white of egg, and especially if these substances are introduced while the animal is sleeping. Of particular interest is the long latent period then intervening between the moment of feeding and the time when the first drop of gastric juice is obtained. Even in the case of raw meat, 15 to 45 minutes may elapse before the secretion actually begins, but a somewhat quicker reaction may be evoked by giving these substances in a semi-digested condition, because the purely nervous excitation is then augmented by the liberation of chemical bodies in the form of vitamins and hormones which stimulate the gastric glands either directly or through the blood.

A slight secretion of gastric juice is also obtained after the stomach has been isolated from the central nervous system by the division of all of its nerves, namely, the vagi and splanchnic nerves and the communicating rami of the latter. Consequently, this organ must be in possession of a local reflex mechanism which under ordinary conditions is controlled directly by the central nervous system. In other words, inasmuch as the stomach is a typical autonomic organ, the higher centers merely alter its activity in accordance with the functional requirements of other parts of the body. Impulses are relayed to it which either increase or decrease the flow of gastric juice.

These data tend to show that the direct stimulation of the gastric receptors is not a very efficient means of evoking a secretion of gastric juice. Much better results may be obtained by influencing the local mechanism through a more general mechanism which is capable of introducing what is termed the psychical element, or appetite. As long ago as 1852, Bidder and Schmidt observed that a copious secretion of gastric juice may be evoked in a dog with a gastric fistula by simply allowing him to obtain a visual impression of the food. Some years later Richet obtained the same results in a boy whose esophagus had been completely closed by a cicatrix formed in consequence of an erosion by a strong alkali. Since that time this observation has been repeated a large number of times both upon human beings with gastric fistulas as well as upon different mammals with diverticulated stomachs. Another procedure which has led to valuable results is

the method of sham-feeding.¹ Having established a gastric fistula, the esophagus is divided in the neck and its two cut ends securely fastened to the edges of the wound. The animals so changed soon accommodate themselves to their new conditions and can then be subjected to:

(a) Actual feeding through the distal orifice of esophagus.

(b) Sham-feeding, by allowing them to masticate the food in the usual way, although it again reaches the outside through the opening in the neck.

(c) Psychical feeding, in which the animal is merely allowed to see or to smell the food without actually ingesting it.

The importance of the psychical element in the formation of gastric juice may be proved in various ways.² Thus, it suffices to allow the hungry animal to see the food; moreover, the secretion then obtained is usually more copious than if secreted without the help of psychic impressions. For example, if two dogs are fed weighed amounts of meat through fistulas, without their knowledge, a certain quantity of gastric juice will be secreted by each, but if one of these animals is now given a sham meal of meat, the amount of protein digested by it in a given period of time will be five times greater than that digested by the other animal not psychically stimulated. Those investigators who have studied the effects of gastric fistulæ in human beings, have made similar observations and maintain that the seeing, smelling and thinking of palatable food, as well as the leisurely mastication of sapid substances, give rise to a copious flow of gastric juice. Appetite is a potent factor in this process and so is the quality of the food. Food and condiments which the individual liked especially, were more effective than, say, butter, bread and meat. This fact may serve as a reason for the ingestion of a palatable dessert, salad, or fruit at the end of a meal. The purpose of these "appetizers" is to augment and to prolong the appetite secretion of gastric juice.³

The fact to be deduced from these experiments is that the different kinds of food possess an almost specific stimulating power which enables them to vary not only the quantity of the gastric juice, but also the length of the period intervening between their ingestion and the appearance of the secretion. In the case of saliva it is easily observed that this latent period is short, a fact which is in keeping with functional requirements. Evidently, since the food enters the mouth quickly and remains here for only a relatively short period, it is essential that this secretion be produced in the shortest possible time. In the case of gastric juice an urgency of this kind does not exist and hence, the latent period may be appreciably prolonged.

¹ Pawlow and Schumowa-Simanowskaja, *Zentralbl. für Physiol.*, iii, 1889.

² Bogen, *Pflüger's Archiv*, cxvii, 1907.

³ Rabinowitch, *Dissertation*, Giessen, 1907 (spices); Pinkussohn, *Münch. med. Wochenschr.*, 1906 (coffee and cocoa); Kast, *Archiv für Verdauungskr.*, xii (alcohol); Bickel, *Berliner klin. Wochenschr.*, 1906 (mineral waters).

Thus, a meat diet does not give a maximum rate of secretion until the end of the first or second hour, while a bread diet produces its secretory climax during the first hour, and a milk diet during the second and third hours. Quite similarly, large quantities of oil diminish the secretion considerably, while starch, fat, and white of egg are practically inert. It has also been observed that meat-juice is a more efficient stimulus than bread-juice, while milk-juice occupies in this regard an intermediate position. Contrariwise, bread-juice contains a more abundant quantity of ferment than meat-juice. Among the influences which depress the secretion of gastric juice might be mentioned unpleasant emotions, such as anger, and fear. Thus, it has been noted that dogs with gastric fistulas cease secreting when confronted by a cat, and we are all well aware of the fact that a clear conscience and untroubled mind are essential prerequisites for an efficient gastric digestion.

While it is difficult to combine these facts into a brief story of events, it may be stated that the normal secretion of gastric juice is dependent upon two factors, namely, upon an immediate nervous and a latent chemical stimulus. The former finds its origin in the excitation of the receptors of the oral cavity as well as of certain exteroceptors, such as the retinae and the olfactory cells, and its purpose is to produce a flow of gastric juice in as short a time as possible after the ingestion of the food. This gives rise to what has been termed the appetite secretion. The purpose of the second factor is to maintain this secretion after it has been initiated. In the latter instance, the stimulus is of intragastric origin, and is evoked by the vitamins of the food and the specific hormone, gastrin. The most important reaction is the first, or appetite secretion, because it serves to establish a digestive medium for those food stuffs which in themselves are very inefficient gastric stimulants. In accordance with this sequence of events, it may be said that the gastric juice which is secreted in the course of a meal, consists of two portions, namely, (a) an initial amount which is poured forth within 5 minutes after the ingestion of the food and which is due to a reflex stimulation, and (b) a latent amount, the secretion of which follows the chemical stimulation by the food after it has entered the stomach.

The Duodenal Juice.—Beginning at the pylorus, the gastric glands gradually pass over into the glands of Brunner. The latter are imbedded in the submucous coat, and appear as branched and convoluted tubes, the ducts of which open free upon the mucous surface. In the carnivora, they occupy an area extending about 3 to 5 cm. below the pylorus, while in the herbivora they reach to a line about 15 cm. below this point. The secretion furnished by them is known as the duodenal juice. It is alkaline in reaction, owing to its content in carbonates, and effervesces strongly when brought in contact with an acid. Its action as a digestive juice is not important, although it contains some *invertin* which inverts cane-sugar, as well as some

erepsin. Its importance lies rather in the fact that it gives lodgment to a substance, known as *enterokinase*,¹ which possesses the power of greatly augmenting the action of the pancreatic juice on proteins. In the absence of this secretion, following, for example, the resection of extensive segments of the duodenum, serious digestive disturbances result; in fact, it is commonly stated that this operation is fatal for reasons not fully understood. It is supposed, however, that it converts the inactive trypsinogen into the powerful proteolytic agent trypsin. A similar activating enzyme has been abstracted from the spleen (Mendel), but it has not been proved that this organ exerts this particular function under normal conditions.

The Pancreas.—This gland is tubulo-racemose in its character, the individual acini being separated from one another by a loose net-

FIG. 495.—DIAGRAM TO SHOW THE POSITION OF THE DUCTS OF THE PANCREAS.

D, Duodenum; P, pancreas; DC, ductus choledochus; DW, ductus Wirsungianus; DS, ductus Santorini.

work of connective tissue in which are imbedded small groups of spindle-shaped cells forming the so-called islets of Langerhans. It will be brought out later on that these cells furnish an internal secretion which has to do with the metabolism of the carbohydrates. For the present we are concerned solely with the true secretory cells of this organ, forming the typical tubular acini and producing the "external" secretion known as the pancreatic juice. These cells are polyhedral in shape and exhibit two zones, namely, a clear outer and a granular inner. Their strongly basophile nuclei occupy a central position within their cytoplasm.

It will be remembered that this organ forms a narrow band of tissue, the central portion of which partially envelops the duodenum, while its caput and cauda extend for some distance into the mesentery. Its principal excretory channel is the pancreatic duct or duct of Wirsung, which opens into the duodenum about 10 to 12 cm. below the sphincter of the pylorus. A smaller duct may also be present, which is known as the duct of Santorini and drains the head-region of this organ, entering

¹ Chepowalnikow, Dissertation, St. Petersburg, 1899.

the duodenum separately at a distance of 2 to 3 cm. above the former.¹ In some animals the duct of Wirsung unites with the common bile duct shortly before its entrance into the duodenum. This accounts for the fact that tumors, affecting the head and body of the pancreas, very frequently give rise to a stagnation of the bile. Thus, a slowly developing jaundice, which is associated with a loss of appetite and indigestion, but no pain, almost always indicates a carcinoma of the pancreas.

In the dog, the blood-supply of the pancreas is derived from the mesenteric, pancreatico-duodenal and splenic arteries. The first supplies its head-region, the second its body, and the third its tail. The venous return is effected by three channels of which the vena pancreatica is the largest. The latter joins the portal vein a short distance below the hilum of the liver. A small portion of its blood is returned by way of the splenic and mesenteric veins, but this also enters the portal vein. The nerve-fibers innervating this organ arise in the mesenteric and celiac ganglia of the solar plexus and follow the highways of the aforesaid arteries. Pre-ganglionically, connection is made with the central nervous system by way of the vagi and splanchnic nerves.

Histological Changes in the Cells of the Pancreas During Secretion.—In 1856 Cl. Bernard observed in fresh preparations of the pan-

FIG. 496.—A TERMINAL LOBULE OF THE PANCREAS OF THE RABBIT. (*Kühne and Sheridan Lea.*)

A, in resting condition; B, after active secretion.

creas of the rabbit that two-thirds of the inner zone of its cells are taken up by a dense granular material which he believed to be the mother-substance of the active principles of the pancreatic juice. Later on Kühne and Lea² succeeded in showing that the activity of this gland is associated with a loss of at least a part of this material. The cells become smaller in size and eventually exhibit a perfectly clear basal zone. While these changes may be rendered more conspicuous by the use of pilocarpin and secretin, their complete development frequently necessitates several injections of these drugs until the flow of pancreatic juice has almost ceased, owing to an exhaustion of the secretory material. While the normal gland possesses a yellowish-white color, it then becomes transparent, soft, and pink in color.

Methods Employed to Procure Pancreatic Juice.—The best way in which pancreatic juice may be obtained, is to establish a fistula

¹ Opie, *Diseases of the Pancreas*, London, 1903, and Gegenbaur, *Anatomie des Menschen*, Leipzig, 1899.

² *Unters. aus dem physiol. Inst. zu. Heidelberg*, 1882.

between the duct of Wirsung and the outside. Cl. Bernard advocated the use of a lead or silver cannula which he inserted in the orifice of this duct and secured in the sides of the abdominal wound. A more convenient and permanent method has been devised by Heidenhain and modified by Pawlow. It makes use of the fact that in the dog the

FIG. 497.—ALVEOLI OF DOG'S PANCREAS, CELLS LOADED: OSMIC PREPARATION. (*Babkin, Rubaschin, and Ssawitsch.*)

lower duct is larger than the upper and has a well-defined orifice. A quadrilateral piece of the intestinal wall immediately surrounding this orifice is resected and is fastened in the sides of the abdominal wound. The integrity of the duodenum must of course be reëstab-

FIG. 498.—ALVEOLI OF DOG'S PANCREAS AFTER A PERIOD OF ACTIVITY PRODUCED BY APPLICATION OF ACID TO MUCOUS MEMBRANE OF DUODENUM. (*Babkin, Rubaschin, and Ssawitsch.*)

lished before the latter is completely closed. Inasmuch as the pancreatic secretion possesses strong proteolytic properties, the external wound must be kept dry and clean, otherwise erosions and infection will result. Furthermore, since the establishment of this fistula prevents a large portion of the pancreatic juice from entering the

intestine, an animal of this kind frequently suffers from indigestion and metabolic disturbances leading to a loss of weight and severe general symptoms. But since this disarrangement involves chiefly the digestion of the proteins, it may be obviated in a measure by the feeding of abundant quantities of milk to which sodium bicarbonate has been added.

The Character of the Pancreatic Juice.—It is a clear, watery and slightly opalescent fluid, possessing a specific gravity of from 1.007 to 1.009. Moreover, since it contains considerable amounts of phosphates and carbonates, and especially those of sodium, its reaction is strongly alkaline. When its flow is stimulated by means of secretin, about 30 to 50 c.c. of it may be obtained in the course of an hour and from 300 to 500 c.c. in a day. Its composition¹ is as follows:

Total solids.....	1.6 -1.56 per cent.
Total protein.....	0.5 per cent.
Ash.....	1.0 -0.96 per cent.
Chlorids.....	0.28-0.29 per cent.
Total nitrogen.....	0.73 per cent.

The organic substances contained in it are enzymes, a small amount of protein material, and traces of leucine, tyrosine, xanthine, and soaps. Pancreatic juice contains four enzymes namely:

(a) Trypsin, proteolytic or proteoclastic in its nature (Purkinje and Pappenheim, 1836). Enterokinase converts trypsinogen into trypsin. Erepsin is present sometimes.

(b) Amylase; amylopsin, amylolytic in its nature (Valentin, 1844).

(c) Lipase; steapsin, fat-splitting, lipolytic or lipoclastic in its nature (Cl. Bernard, 1846), and a

(d) Milk-curdling substance.

The Regulation of the Secretion of Pancreatic Juice.—It is commonly held that the pancreas of the carnivora secretes intermittently, the immediate cause of the secretion being either nervous or chemical in its nature. In the herbivora, on the other hand, the secretion is constant, a condition which is in accord with the rather continuous character of their digestion. If brought about in a reflex way, the stimuli arise in the forepart of the alimentary canal and are relayed to the pancreas by way of the vagus nerve which contains secretory fibers for this organ. The fact that a reflex circuit of this kind exists seems proven, because the stimulation of the medulla oblongata is usually followed by a copious flow of pancreatic juice. A similar effect may be obtained by psychic stimuli as well as by the stimulation of the central end of the divided lingual nerve.² But the early attempts of Heidenhain to localize the secretory fibers of the pancreas in the vagus failed completely, because the stimulation of this nerve gives rise to cardio-inhibition and a fall in blood-pressure which cause the

¹ DeZilwa, Jour. of Physiol., xxxi, 1904, 230, and Wolgemuth, Bioch. Zeitschr., xxxix, 1912, 321.

² Pfüger's Archiv, x, 1875, 606.

extremely sensitive epithelium of this organ to cease secreting. Later on Pawlow conceived the idea of permitting the cardiac fibers of the vagus to degenerate before attempting to test the power of this nerve upon the pancreas. In all these cases, the stimulation of the distal end of this nerve, 3 or 4 days after its division, evoked a copious flow of pancreatic juice, but in spite of the fact that the existence of these reflex paths has been thoroughly established, no definite statements can be made at this time regarding the relative importance of the nervous and chemical stimuli. At all events, the impulses from the mouth as well as those of psychic origin seem to play a less important part in the secretion of pancreatic juice than in that of gastric juice.

Inasmuch as a formation of pancreatic juice also takes place after the pancreas has been completely isolated from the central nervous system, Popielski¹ came to the conclusion that this organ embraces a local nervous mechanism which is sufficient for its activity. The claim was then made by Dolinsky² and Pawlow that the active factor involved in this secretion is the acid of the gastric juice which exerts its peculiar action as soon as the chyme is discharged into the duodenum. In substantiation of this contention Popielski proved later on that the injection of an acid into a segment of the duodenum gives rise to a copious flow of pancreatic juice even after both vagi nerves and the ramifications of the solar plexus have been cut. This fact immediately disposed of the contention that the acid stimulates the duodenal mucosa and thereby sets up certain afferent impulses which are finally relayed to the pancreas by way of the corresponding fibers of the vagus system. On repeating these experiments, Bayliss and Starling³ discovered that a secretion of pancreatic juice also results if the acid is introduced into a loop of duodenum which had previously been isolated from the rest of the body by dividing all its nervous connections. This result showed very clearly that a chemical stimulus must be at work which affects the pancreatic cells through the blood stream. In further substantiation of this view these authors found that an acid, when injected into the portal vein, remains without effect, while an acid infusion of the mucous membrane of the duodenum, when neutralized and injected into the same channel, gives rise to a copious flow of pancreatic juice. These tests were then controlled by the use of similar extracts of other organs, but none of these yielded positive results.

The conclusion to be derived from these data is that the activity of the pancreas is also under the control of a hormone which originates in the mucosa of the duodenum and upper small intestine. This agent is called secretin. It should be noted, however, that it is not present as such in these cells, but is held in them in an inactive form to which the name of pro-secretin has been given. In consequence of the

¹ *Centralbl. für Physiol.*, x, 1896, 405, and xix, 1906, 801.

² *Dissertation*, St. Petersburg, 1894.

³ *Jour. of Physiol.*, xxviii, 1902, 325.

discharge of the acid gastric contents, this precursor is changed into the active secretin, which is then conveyed to the pancreas in the bloodstream. This organ reacts to it by furnishing an alkaline secretion which in turn neutralizes the acid chyme, thereby setting a limit to the formation of secretin. The succeeding discharge of chyme gives rise to another stimulation by secretin, and so on until the stomach is empty. The latter point has been proved by Enriquez and Hallion¹ in this way. An anastomosis was formed between the arteries and veins of two dogs. Cannulas having been inserted in the pancreatic ducts of both animals, one of them then received an injection of a dilute acid into the duodenum. Peculiarly enough, a copious secretion of pancreatic juice resulted in both animals. This experiment proves very clearly that secretin is a true chemical messenger and is actively engaged in the formation of normal pancreatic juice.

Inasmuch as it has been noted that secretin produces at first a very copious flow, which, however, is soon greatly diminished, and that a second dose of this agent does not evoke so pronounced an effect as the first, it may be conjectured that this hormone possesses the function of exciting the pancreatic secretion in the shortest possible time. Accordingly, it may then be assumed that it is the purpose of the nervous mechanism to sustain this secretion as long as required. This view finds support in the fact that the secretion obtained upon stimulation of the vagus nerve is characterized by a long latent period, and that the vagus-juice is less watery but contains a larger amount of organic matter than the secretin-juice. In analogy with salivary and gastric secretion, these differences may be explained by assuming that the nervous and chemical factors just mentioned affect different constituents of the pancreatic acini, one of them, possibly, stimulating the cells of the acini proper, and the other the cells nearer the excretory duct.

The chemical nature of secretin is still unknown. It is not a ferment and may be prepared in the following manner: The mucous membrane of the duodenum is ground up with sand and boiled with 0.4 per cent. hydrochloric acid. The filtrate contains the secretin. It is rendered neutral under addition of sodium hydrate. Dale and Laidlaw² harden the mucosa in HgCl_2 , boil it, reject the filtrate and extract the residue with a 2 per cent. solution of acetic acid, containing 1 per cent. of HgCl_2 . The filtrate is precipitated by the addition of NaOH to the neutral point. Secretin is stable in acid solutions, but is rapidly oxidized in alkaline, and neutral solutions. Its action is not destroyed by atropin, although this agent paralyzes the secretory mechanism of the vagus. In this connection, brief reference should also be made to the fact that a flow of pancreatic juice may be excited by means of pilocarpin, Witte's peptone, and curarin (Popielski).

¹ Compt. rend., lv, 1903, 233.

² Proc. Physiol. Soc., Jour. of Physiol., xlv, 1912.

CHAPTER LXXX

THE DIGESTIVE SECRETIONS (CONTINUED)

C. BILE AND INTESTINAL JUICE

The Liver.—The liver is the largest gland in the body, and is in origin a tubular gland which, in the course of its development, has lost much of its original character. It is made up of rounded masses or lobules which measure about 1.0 mm. in diameter and are composed of columns of cells radiating from a common center. These cells possess a spheroidal shape but have in many cases become polygonal on ac-

FIG. 499.—DIAGRAMMATIC REPRESENTATION OF THE BLOOD SUPPLY OF THE LIVER ACINI.

P, Portal terminal; *JV*, interlobular veins; *CV*, central veins which are eventually collected in the hepatic vein; *HA*, hepatic arteriole, the interlobular capillaries of which empty into the portal terminals; *B*, biliary capillary which begins as biliary space between the hepatic cells.

count of their being packed so closely together. Their cytoplasm contains a rounded and centrally placed nucleus, as well as fatty particles, and variable amounts of glycogen.

The blood supply of this organ is derived from two sources, namely from the hepatic artery and the portal vein. The former supplies its reticular network, *i.e.*, the tissue of the extra- and interlobular spaces, while the latter nourishes the

hepatic cells themselves. Eventually the capillaries of the hepatic artery unite into channels which empty directly into the terminals of the portal vein at the periphery of each lobule. So united they form the central or intralobular veins, and these in turn the hepatic veins. This anastomosis between the hepatic arterial and portal systems accounts for the fact that the secretory power of this organ cannot be destroyed by the ligation of the aforesaid vein. Under these circumstances, the arterial blood finds its way in greater quantity into the portal channels, thereby compensating in part for the loss of the portal blood.¹

The nerve supply of the liver is derived from the celiac ganglion of the solar plexus. The individual postganglionic fibers ascend along the hepatic artery around which they form an intricate plexus. At the hilum of this organ they ramify extensively, forming here the so-called hepatic plexus. Distally to this point they follow the branches of the hepatic artery in order to gain the interior of the different lobes of this organ.

Of special interest to us at this time is the fact that the hepatic cells lie in direct contact with these intralobular capillaries, and furthermore, since the lining of these vessels is in many places deficient, the blood is brought into direct communication with the contents of these cells. These deficiencies account for the fact that perfectly intact red corpuscles may be found inside their cytoplasm. Here and there along these vessels we also note the so-called stellate cells of Kupffer which are large phagocytic bodies capable of ingesting red cells and other solid particles contained in the blood. Hence, it cannot surprise us to find that coloring fluids injected through the portal vein may be traced directly into the interior of these cells where they produce delicate canaliculi or sinusoids. In this organ, therefore, the lymph does not play the part of a middle-man between the blood and the cells.

On the other side of these radial rows of secretory cells are the biliary spaces and capillaries which convey their characteristic secretion, the bile, into the larger collecting channels. While many histologists state that these delicate tubules arise in secreting vacuoles within the cytoplasm of these cells, others claim that they begin as blind spaces between two adjoining rows of cells. Farther outward they acquire a lining of columnar epithelium as well as a basement-membrane and fibrous and smooth muscle tissue. In many animals, the larger biliary ducts empty into a special reservoir which is known as the gall-bladder. The liver is also plentifully supplied with lymphatics which accompany the capillaries of the portal vein as well as those of the hepatic artery. These two systems communicate

FIG. 500.—DIAGRAM TO ILLUSTRATE THE RELATION OF THE PORTAL TERMINALS (P) TO THE BILIARY CAPILLARIES (B). THE ARROWS INDICATE THE DIRECTION OF THE FLOW.

¹ Burton-Opitz, Quart. Jour. of Exp. Physiol., iv, 1911, 93.

with one another at the periphery of the lobule as well as near the hilum.

The Function of the Liver.—While we are chiefly concerned at this time with the external secretion of the liver, known as the bile, it should not be forgotten that this organ performs several other important functions which may be briefly summarized as follows:

(a) It furnishes an internal secretion which is concerned with the metabolism of the carbohydrates. Sugar is deposited in the hepatic cells in the form of glycogen, which is later on reconverted into sugar.

(b) It forms those bodies which are subsequently abstracted by the cells of the kidney and appear in the urine in the shape of urea and allied substances.

(c) It is the principal organ in which the red blood-corpuscles are destroyed.

(d) It plays an important part in the coagulation of the blood, because it gives rise to anti-coagulating substances.

FIG. 501.—LIVER CELLS CONTAINING GLYCOGEN. (Barfurth.)

(e) While its external secretion, the bile, possesses an important digestive action upon the fats, it is also a natural antiseptic, an excretory medium, and a stimulant of peristaltic activity.

(f) It is the chief heat-conserving organ in our body, and probably also

(g) The principal formant of lymph.

The Characteristics of Bile.—The quantity of bile which is secreted by an adult of medium weight in a day, has been estimated at 500 to 1000 c.c. It is not difficult to obtain it, because the establishment of a fistula of the common duct or of the fundus of the gall-bladder is frequently undertaken to-day for the relief of the symptoms following the obstruction of these passages by calculi or by malignant growths affecting the pancreas and neighboring orifices of the duct of Wirsung and common bile duct. Bile may also be obtained from the gall-bladder after death, but if removed days later, it may have lost its normal characteristics altogether. In the dog, Pawlow advises to establish a biliary fistula by excising the entire segment of duodenum in the immediate vicinity of the orifice of the common duct, and fastening it to the edges of the wound in the abdominal wall.

Fresh human bile, as well as that of the carnivora, is golden red in color, but changes into dark green on exposure. Evidently, it must contain a number of pigments which are rather unstable and are altered by oxidation. The bile of the herbivora is greenish in color. When fresh, it is very bitter, and has a slimy consistency, due to its content in mucin. The latter peculiarity, however, is imparted to it not by the hepatic cells but during its passage into the gall-bladder. This fact, that bile withdrawn from the hepatic duct and its tributaries is normally clear, is of some functional importance, because if it were not, its flow might be greatly retarded. Thus, we find that in extreme cases of biliary catarrh the larger bile ducts are frequently blocked by mucous plugs, this stagnation of the bile giving rise to an absorption of its pigments and the complex of symptoms constituting jaundice or icterus. The viscosity of bile is 1.8 times as great as that of distilled water at 37° C.¹ It is usually neutral or faintly alkaline to litmus. Perfectly clear bile possesses a specific gravity of 1.008 to 1.010, while that collected directly from the gall-bladder may present a value of 1.030 and over.

The bile of all animals contains pigments, salts and cholesterol. In accordance with Hammarsten,² human bile obtained from a fistula of the hepatic duct possesses the following composition:

Water	97.48
Solids.....	2.52
Bile salts.....	0.93
Taurocholate.....	0.30
Glycocholate.....	0.63
Fatty acids.....	0.12
Mucin and pigments.....	0.53
Cholesterol.....	0.06
Lecithin and fat.....	0.02
Soluble salts.....	0.81
Insoluble salts.....	0.02

The bile collected directly from the gall-bladder is more concentrated than that withdrawn from the hepatic duct. This difference is usually said to be due to an absorption of its water, but is caused in reality by an ingo of material from the cells lining the outer biliary passage. In this way mucin, phosphoprotein and some cholesterol are added to the hepatic bile. It has been shown, however, that the mucin of the bile of the ox, dog and sheep is not a true mucin, because it does not yield a carbohydrate group on being boiled with dilute acid, and is rather rich in phosphorus. It is in reality a representative of the phosphoproteins and seems to have no other function than that of anointing the surfaces of the biliary channels and intestines. The mucinoid material in human bile is true mucin.

The amount of bile secreted in a day is estimated at 525 c.c., but since this value has been obtained from cases of biliary fistula, it cannot serve as anything more than a general guide.³ Bile is secreted continuously, but not at a perfectly uniform rate, because it is produced in smaller amounts during the early morning hours and in greatest quantity after the noon-day meal.

The Storage of Bile.—In the majority of animals the bile is collected by the hepatic duct which is then united with the cystic duct to form the common duct, or ductus choledochus. In man, the latter opens into the duodenum about 10 to 12 cm. below the pylorus, where it meets the pancreatic duct or duct of Wirsung to form a papillary prominence. Obviously, this arrangement allows of a thorough mix-

¹ Burton-Opitz, *Bioch. Bull.*, iii, 1914, 35.

² *Ergebn. der Physiol.*, iv, 1905.

³ Pfaff and Balch, *Jour. of Exp. Med.*, ii, 1897, 49.

ing of these secretions. The cystic duct is enlarged peripherally into a vesicular receptacle, known as the gall-bladder, but this diverticulum is not present in all animals, its place being taken by the biliary ducts themselves which are then distended into tubular pouches. A similar enlargement of these ducts results in those human beings who have had their gall-bladder removed for the relief of malignant and other affections of this organ. Moreover, it should be noted that those animals which are not in possession of this storehouse for bile (horse), show a rather continuous digestive activity and require, therefore, a more constant supply of bile.

This is not the case in the carnivora, and hence, the bile is stored in these animals during the periods intervening between the successive periods of digestion. Thus, while the hepatic cells furnish a constant supply of bile, the latter is not conveyed directly into the duodenum, but is diverted through the cystic duct into the gall-bladder. Its storage is made possible by the fact that the orifice of the common duct is guarded by a transverse band of smooth muscle tissue which acts as a sphincter and prevents its constant escape. Naturally, the continuous influx of bile from the hepatic duct gives rise to a gradual distention of the gall-bladder until a stimulation results which relaxes this sphincter and relieves this organ of its contents. Thus, we are really in possession of two separate mechanisms, one for the secretion and one for the storage and expulsion of the bile.

According to Burton-Opitz,¹ the gall-bladder is innervated by fibers derived from the celiac ganglion of the solar plexus which ascend along the small artery, supplying this organ and neighboring region of the liver. Their function becomes evident if it is remembered that the wall of this receptacle is made up in part of smooth muscle tissue which on contraction lessens its lumen and subjects its contents to a moderate pressure. The latter, however, rarely exceeds 5.0 mm. Hg, but evidently, a greater expelling force is not called for, owing to the fact that practically no resistance need be overcome. The pressure at the orifice of the common duct is about zero, unless raised momentarily by peristalsis, so that the only other prerequisite for a free discharge of the bile is the relaxation of the sphincter. It may rightly be concluded that the contraction of the gall-bladder coincides with the relaxation of the latter, although it is not definitely known how this simultaneous action is brought about. It has been established, however, that it takes place shortly after the entrance of chyme into the duodenum, *i.e.*, generally during the third hour after a meal, but no clear picture can be drawn of the mechanism involved in this process. For the present, therefore, it must be regarded as a reflex evoked in the duodenum, the local nerve paths of which are contained in the plexus celiacus, plexus hepaticus and plexus gastroduodenalis. Preganglionically, the motor fibers of the gall-bladder

¹ Am. Jour. of Physiol., xlv, 1917, 62.

have been detected in the vagus and greater splanchnic nerves, but no very convincing data have been obtained.¹

The Formation of Bile.—It has been stated above that the bile is secreted continuously but not at a uniform rate. Naturally, this variation is dependent upon intermittent stimuli, such as result whenever the stomach ejects its contents into the duodenum. This fact suffices to show that the hepatic cells are under the control of a mechanism which regulates their activity. The latter may be either nervous or chemical in its nature. Thus, it may be assumed that the liver is in possession of secretory fibers which arise in the celiac ganglion and reach this organ by way of the hepatic plexus. But since a reflex contraction of the gall-bladder and a more copious flow of bile may also be evoked by the introduction of an acid into the duodenum, and since these effects may also be obtained after the liver has been isolated from the central nervous system by the division of its nerves, it has been concluded that the secretion of bile is also regulated by a specific hormone. Starling recognizes in this chemical stimulant the secretin of the duodenal mucosa, his claim being based upon the fact that the injection of this agent into the blood stream evokes a copious flow of bile. We shall see later on that secretin also excites a secretion of intestinal juice, and hence, it may be held that it serves as the initial stimulus for three of the principal digestive fluids.

Inasmuch as the hepatic cells derive the material from which they form the bile from the portal vein, their activities must be adjusted to a very low secretory pressure. It has been shown by Burton-Opitz² that the blood arrives in the tributaries of the portal system of the dog under a pressure of about 12 mm. Hg and enters the hilum of the liver under a pressure of 9 mm. Hg. In the cat, the pressure encountered at this point amounts to only 7 mm. Hg. Now, since the pressure in the inferior vena cava opposite the orifices of the hepatic veins is practically zero, a pressure of about 9 mm. Hg must suffice to drive the blood through the portal terminals. This is the pressure under which the hepatic cells perform their secretory function. The blood of the hepatic artery, on the other hand, arrives at the liver, say, under a pressure of 100 mm. Hg, which is used up very largely in its task of overcoming the resistance in the interstitial capillaries. Both types of blood then traverse the intralobular veins, that of the portal vein furnishing the secretory material, and that of the hepatic artery the oxygen.

If the general blood pressure is reduced, the quantity of bile secreted is diminished, while its percentage of solids is increased. This same effect may be produced by the excitation of the vasoconstrictor fibers of the liver or by the ligation of several branches of the portal

¹ Bainbridge and Dale, *Jour. of Physiol.*, xxxiii, 1905, 138; Doyon, *Archives de physiol.*, 1894, and Freese, *Bull. Johns Hopkins Univ. Hosp.*, xvi, 1905.

² *Quart. Jour. of Exp. Physiol.*, vii, 1913, 57.

vein. These facts clearly show that the secretion of bile is closely dependent upon a proper secretory pressure. It should be noted, however, that the formation of bile takes place in accordance with the same principles as the formation of other secretions; *i.e.*, it is not due to filtration alone but also to osmosis, diffusion, and a certain vital activity on the part of the hepatic cells. To prove this point, it may be shown that these cells are able to secrete against a higher pressure than the portal blood pressure. Thus, if a cannula is inserted in the common duct which in turn is connected with a narrow vertical glass tube, the bile will rise in this tube until its height equals a pressure considerably above that prevailing in the portal vein at the hilum of the liver. How rapidly this level will be reached differs with the general condition of the animal. In a robust cat under ether, probably 30 to 60 minutes will be required before the pressure in the common duct will have risen to 15 mm. Hg, which equals twice the pressure ordinarily encountered in the portal vein of this animal. In the dog, a pressure of 15 to 20 mm. Hg may be established before the secretion of bile ceases. Clearly, since the hepatic cells are capable of secreting against a pressure higher than that under which they obtain their material, filtration cannot be the only factor concerned in this process.

A very good proof of the secretory power of the hepatic cells is also furnished by the fact that the constituents of the bile are not brought to the liver in their complete form but are formed here from their precursors. Lastly, it is possible to vary the secretion of bile by chemical agents which act in the manner of secretagogues, and stimulate the cells directly. These bile-driving substances are known as *cholagogues*. While aloes, calomel, peptone and salicylates may be used for this purpose, the most powerful agent is the bile itself. Schiff, however, has shown that if the bile is administered by the mouth or through an intestinal fistula, a considerable portion of it is absorbed. Thus, at least a part of the cholagogic action of the constituents of bile may be due to the fact that the material absorbed is again made use of in the formation of new bile. To prove this point Wertheimer¹ injected sheep's bile into the mesenteric vein of a dog and was able to demonstrate the presence of cholehematin in the bile of this animal. This body occurs normally only in the bile of the sheep.

Icterus. Cholemia. Resorption of Bile.—While it cannot be doubted that the hepatic cells are capable of secreting against a higher pressure than that prevailing in the portal vein, this process cannot be continued indefinitely. The upper limit having been reached, the secretion ceases and some of the constituents of the stagnated bile pass over into the circulation. This resorption gives rise to the condition of icterus or jaundice, which is characterized by a deposition of the biliary pigments in the tissues of the body, causing a yellow

¹ Archive de physiol. norm. et path., 1892, 577; Stadelman, Zeitschr. für Biol., xvi, 1897, 1; Whipple and Hooper, Am. Jour. of Physiol., xl, 1916, 349.

discoloration of the sclera, conjunctiva and mucous surfaces. This pigmentous material also appears in the urine and finally gives rise to a reduction in the frequency of the heart and respiration and a general bodily and mental fatigue.

A condition of this kind may arise in consequence of a catarrhal inflammation of the larger biliary passages and the formation of mucous plugs, or in consequence of the escape of a calculus from the gall-bladder which later on becomes firmly wedged in between this organ and the duodenum. Under these circumstances the feces assume a grayish color and the consistency of clay, owing to the absence of bile and the resultant accumulation of much undigested fat. Defecation becomes infrequent and labored, owing to the loss of the tonic of the intestinal musculature and the solidity of the fecal material. Jaundice may also be incited by the administration of poisons which, however, do not produce an actual obstruction of the larger biliary passages. The cause of this non-obstructive type of icterus is more difficult to explain, unless it is held that the poison gives rise to an erosion and obliteration of the intralobular channels. This result is quite common in all conditions producing an excessive destruction of red cells. It is generally believed that this resorption of bile takes place through the lymphatics and not through the blood-capillaries,¹ because the ligation of the common duct does not give rise to jaundice if the thoracic duct is obstructed at the same time.

Extirpation of the Liver.—It has previously been shown that the secretion of bile is dependent upon filtration, diffusion and osmosis, and a vital activity of the cells. Attention has also been called to the fact that bile is secreted continuously but not at a uniform rate, because different stimulations result from time to time which vary its formation. Chief among these is the chyme which, upon its ejection into the duodenum, evokes a local reflex and liberates the hormone secretin. By this means the increased activity of the hepatic cells is made to coincide precisely with the evacuation of the gall-bladder, so that both processes occur at about the third hour of digestion and synchronously with the outpouring of the pancreatic juice. In this connection it is of interest to note that the digestive products of the proteins and fats evoke a much more copious flow of bile than the carbohydrates. It may also be increased by a large intake of water, and diminished by hunger and emotions.

The ligation of the portal vein does not stop this secretion altogether, because the hepatic artery is able for a time to compensate for the loss of the portal blood. But this compensation soon proves wholly inadequate to sustain life and the animal succumbs to a vascular depression brought about by the engorgement of the portal circuit.² Much better results may be obtained if an artificial communication is first established between the portal vein and the inferior

¹ Mendel and Underhill, *Am. Jour. of Physiol.*, xiv, 1905, 252, and Eppinger, *Ziegler's Beitr.*, xxxi, 1903, 230.

² The ligation of the portal vein distally to the orifice of the pancreatic vein does not prove fatal, because the blood of the mesenteric veins then flows into the splenic vein, whence it reaches the gastric veins and the hilum of the liver by way of the pancreatic veins. This reversal of the splenic blood stream is made possible by the enlargement of the small veins upon the pylorus, ordinarily connecting the pancreatic vein with the gastric veins.

vena cava (Eck fistula) by uniting the edges of a longitudinal incision in the wall of the former blood-vessel with those of a similar opening in the latter.¹ In birds, a communication of this kind is normally present in the form of a small channel which connects the capillary expanse of the renal-portal system with the portal vein. Consequently, the portal vein of these animals may be ligated without causing serious disturbances. The total removal of the liver, however, eventually proves fatal, on account of the loss of the necessary amounts of bile and other products of the hepatic cells, such as the precursors of uric acid, salts and pigments. The latter are even more important than the former in spite of the fact that the loss of bile gives rise to serious digestive disturbances. The method of partial and total extirpation of the liver has been made use of more particularly as a means of showing that the special constituents of the bile are actually synthesized in this organ and are not brought to it in their complete form. Naturally, the raw material from which these substances are derived is the blood pigment, hemoglobin. This can be proved either by injecting this substance into the blood stream or by inciting a greater destruction of the red cells by means of hemolytic agents. It will be found that the amount of the corresponding constituents of bile is directly proportional to the destruction of these cells. A similar reduction of the hemoglobin takes place in those tissues which have been the seat of an extravasation. As the hematin of these extravasates is slowly converted into bodies similar to the bile-pigments, the tissues so affected assume different shades of purple, blue and yellow.

It has already been pointed out that the life of the red blood corpuscles is limited and that the "senile" ones are gradually removed from the circulation while they traverse the capillaries of the liver and spleen. But their destruction cannot be accompanied by a discharge of their hemoglobin into the blood stream, because this substance is taken up by the different phagocytic cells, such as the cells of Kupffer lining the intrahepatic spaces. These cells also possess the power of engulfing and destroying the red cells in their entirety, a process which may be more directly studied in the amphibia, because the red cells of these animals contain a sharply differentiated nucleus. In these animals, any excessive destruction of their red cells is invariably followed by an accumulation of a bright green pigment within these phagocytes, which presents all the characteristics of biliverdin. A similar deposition of this material takes place in the neighboring endothelial lining cells as well as in the hepatic cells themselves. These accumulations of pigment may be rendered more conspicuous by staining them with potassium ferrocyanid which colors them blue,

¹ Nencki, Pawlow and Zaleski, *Archiv für Exp. Path.*, xxxvii, 1896, 26; Carrel and Guthrie, *Compt. rend.*, 1906, and Bernheim and Voegtlin, *Jour. of Pharm. and Exp. Ther.*, i, 1909, 463.

or with ammonium sulphid which, owing to their content in iron, colors them dark brown.

Special Constituents of Bile.—The bile contains the sodium salts of complex amino-acids, such as glycocholic, taurocholic, glycocholic and taurocholic. The relative proportion of these salts differs in different animals, glycocholic acid being more abundant in the bile of man and herbivora, and taurocholic acid in that of the carnivora. They are formed as soon as the liver attains its full functional development and do not arise elsewhere in the body. Their detection is made possible by means of Pettenkofer's reaction, which consists in adding a few drops of a 10 per cent. solution of cane-sugar and concentrated sulphuric acid to the suspected liquid. If the latter contains bile salts, a violet ring develops at its point of contact with the reagent. This coloration is due to the formation of an aldehyde-like furfural by the acid from the sugar, and the condensation of this product with the bile salts.

The bile salts may be prepared by mixing fresh bile with about 1 per cent. by weight of animal charcoal. This liquid is evaporated to dryness on the water bath, and the residue powdered and extracted with water and filtered. The filtrate is acidified, but contains, in addition to the bile salts, also some cholesterol, mucin, phosphatides and inorganic salts. Crystallized bile¹ is prepared in the same way, excepting that the dried mixture of charcoal and bile is extracted with boiling absolute alcohol. Since the bile salts are very soluble in alcohol, they are separated out immediately, leaving the other constituents behind. The alcohol is filtered and mixed with absolute ether until a precipitate is formed. On cooling, the bile salts crystallize out, but since they absorb water very readily, they should be kept in a desiccator. The *glycocholic acid* may be hydrolyzed by dilute acids and alkalis and split into glycerin or amino-acetic acid and cholic acid.

In the same way *taurocholic acid* may be split into taurine, or amino-ethyl-sulphonic acid and cholic acid.

It will be shown later on that the bile salts stimulate peristalsis and serve as a vehicle for the digestion of the fats. Their function having been completed, a portion of them is destroyed through the influence of the intestinal microorganisms, while another portion is again absorbed and returned to the liver by way of the portal blood stream. The hepatic cells rebuild this material into new bile salts, thereby greatly reducing their work in synthesizing these salts. A similar "circulation of the bile" between the intestine and the liver is had in the case of some of the derivatives of the pigmentous material of the bile.

Cholic or cholalic acid is a white, crystalline and very bitter substance which is almost insoluble in water, but soluble in alcohol. On addition of water it crystallizes from the latter in rhombic pyramids and tetrahedrons. It is closely allied to cholesterol and may be derived from this substance.

Cholesterol has been found in the bile of almost all animals, but is not present in considerable amounts in human bile (1.6 in 1000 parts). Since it is insoluble in water and solutions of salts, it must seem peculiar that it is dissolved by the bile and may be present here in even greater amounts than normal. This excessive solvent action of bile is due to its content in bile salts and more particularly to the

¹ Platner, Ann. der Chemie und Pharmazie, li, 1844, 105.

cholic acid radicle of the latter, which unites in some way with the cholesterol and keeps it in solution. Little is known regarding the origin of this substance. It may be derived from the food or from the cholesterol of the destroyed red blood corpuscles. Regarding its place of origin, Naunyn makes the assertion that it is eliminated chiefly by the lining cells of the gall-bladder, this statement being based upon the fact that the bile of the latter contains a larger amount of cholesterol than that of the hepatic duct. But since the relative richness of the bladder-bile in this substance may be due to the fact that the cholesterol here secreted is not so easily converted into bile salts, the preceding deduction may not be correct. A disturbance of these oxidations in consequence of traumatism and inflammation of the wall of the bladder, or in consequence of general metabolic disorders (menopause), frequently leads to the formation of gall-stones which may at times occupy every recess of the bladder and also find their way into the large biliary channels. The constant irritation set up by these concretions tends to excite contractions of the bladder which in the course of time mold these masses into many-sided fragments possessing sharp points and sides. As has just been stated, the chief constituent of these concretions is cholesterol (20 to 90 per cent.) to which some desquamated epithelium has been added.¹

The *phospholipins* of bile present themselves principally in the form of lecithin. Practically nothing is known regarding their origin and function. In human bile the lecithin, obtained from the alcohol-soluble material, amounts to 1.7 per cent., but varies considerably in accordance with the character of the food ingested. This fact might lead us to suspect that it is derived from the constituents of the diet, but it may also be true that it originates from the destroyed red blood corpuscles.

The peculiar color of the bile of the carnivora is due to certain *pigments* of which bilirubin is the most important. This substance is unstable and is easily oxidized into a green pigment, known as biliverdin, which in turn gives rise to a whole series of bodies, such as the blue bilicyanin. On further reduction it is converted into urobilin, one of the coloring materials of urine. In the herbivora the chief pigment is biliverdin, but it seems that the aforesaid pigments are interchangeable. *Bilirubin* ($C_{42}H_{56}N_4O_6$) is an iron-free compound and is derived from the hemoglobin of the red corpuscles. Consequently, its formation must be dependent upon the rate of destruction of these cells. Since the bile contains only a trace of iron, it may be surmised that this element is stored in the liver cells to be made use of subsequently in the formation of new hemoglobin. Bilirubin is prepared from powdered red gall-stones by dissolving the chalk with hydrochloric acid and extracting the residue successively with chloroform. The pigment crystallizes from this solution in beautiful rhombic tables or prisms. *Biliverdin* ($C_{32}H_{36}N_4O_8$) is an amorphous iron-free body. It may be formed from bilirubin by oxidation and may be reconverted into this pigment by putrefaction or by the addition of ammonium sulphid. By reduction with sodium amalgam it is changed into hydrobilirubin, a substance identical with stereobilin. Similar reductions go on when the bile pigments reach the intestine, so that they are not recognizable as such in the feces or urine. The most important derivative of bilirubin is stercorubin or urobilin. To this body is due the brown color of the feces. In urine it appears as urobiligen, a colorless substance which is changed into urobilin under the influence of the oxygen of the air. When the bile is prevented from entering the intestine, the urine does not contain this substance.

The Intestinal Glands.—The mucous membrane of the small intestine contains numerous goblet cells, similar in structure to those previously noted in the mucosa of the stomach. Their function is to discharge mucus which serves to lubricate the surfaces of the intestine

¹ Kramer, Jour. of Exp. Med., ix, 1907; Lichtwitz, Arch. klin. Med., xcii, 1907, 100, and Bacmeister, Münch. med. Wochenschr., 1908.

and to render the feces more slippery. In between the different villi, however, the mucous membrane is pervaded by simple tubular glands which are known as the crypts of Lieberkühn. The latter are lined throughout by a single row of columnar epithelium, among which are found a few goblet cells. In the crypts of the large intestine, on the other hand, these mucous cells increase in number and finally displace the secretory cells altogether. This structural change is in complete harmony with the fact that the crypts of the large intestine form only mucus for purposes of lubrication.

The Secretion of the Intestinal Juice or Succus Entericus.—Unadulterated intestinal juice may be obtained by means of a fistula. The method of Thiery (1864) consists in isolating a loop of intestine by two transverse cuts made at some distance from one another.¹ The intervening segment is left in connection with its normal blood and nerve supply and is brought close to the abdominal wall. Its upper end is then closed by sutures, while its lower end is anchored to the sides of the wound in the abdominal wall. The continuity of the intestine from which this loop has been obtained is restored by an end-to-end anastomosis. Vella advises to fasten both ends of the isolated loop to the edges of the wound in the abdominal wall.

The juice obtained from such isolated segments of the small intestine is light yellow in color, opalescent, very watery and strongly alkaline in reaction. It possesses a specific gravity of 1.010, and contains 1.07 per cent. of solids, of which 0.2 per cent. are apportioned to Na_2CO_3 and 0.58 per cent. to NaCl . Its small content in proteins is made up of serum albumin and serum globulin. Its quantity is considerable, a short segment of intestine furnishing as much as 200 c.c. of juice in the course of a day.² One of the commonest means used to excite its flow is to introduce a rubber tube through the fistulous opening, but Pawlow states that the character of the juice is then somewhat different from that obtained without this mechanical stimulation, one of the points of difference being that it contains no enterokinase. Its flow may also be increased by dividing the mesenteric plexus,³ or by producing hydremic plethora.

In the former case, a copious secretion sets in very shortly after the section of these nerve fibers and continues for about 24 hours. Clear at first, the fluid soon becomes cloudy and milky until it assumes the consistency of a thick broth. While

FIG. 502.—DIAGRAM TO ILLUSTRATE THE RELATION BETWEEN THE VILLI AND THE CRYPTS OF LIEBERKÜHN.

V, Villus; G, goblet cells secreting mucus; C, crypt of Lieberkühn; L, lacteal.

¹ Pawlow, *Chirurgie des Verdauungskanales*, *Ergebn. der Physiol.*, i, 1902.

² Frouin, *Compt. rend.*, lvi, 1904, 461.

³ Mendel, *Pflüger's Archiv*, lxiii, 1896, 425.

we might regard this liquid as a true secretory product of the glands of Lieberkühn, it should not be forgotten that a considerable portion of it may be produced by transudation following the relaxation of the intestinal blood-vessels. In general, this phenomenon may be compared to the paralytic secretion of saliva.

The intestinal juice contains several ferments, two of which are proteolytic in their action. Of these *enterokinase* has already been mentioned in connection with the activities of Brunner's glands. The other, which is known as *erepsin*, is present in this juice as well as in almost all tissues of the body. Among the ferments affecting the carbohydrates, may be mentioned *invertase* which transforms sugar into glucose and levulose or fructose, and *maltase* which changes maltose into glucose.¹ Excepting enterokinase, these ferments have also been regarded as intracellular agents and not as constituents of the juice itself. In this form, they should exert their action upon the different foodstuffs while the latter traverse the epithelial cells on their way to the channels of absorption. This contention is founded upon the fact that the liquid obtained by extracting the intestinal mucosa forms a more powerful digestive medium than the intestinal juice itself. In all previous instances, we have observed that a simple extract of the mucosa is inactive, but may be activated very readily by giving to it the reaction which it necessitates. Enterokinase, on the other hand, is not contained as such in the epithelial lining cells but only in the form of a precursor which assumes its activity immediately after its discharge into the general juice of the intestine.

The regulation of this secretion is effected by a nervous as well as a chemical factor. The former is mediated by the peripheral expanse of the autonomic system of this particular region of the body, which presents itself in the form of the plexuses of Meissner and Auerbach. These networks of sympathetic fibers are situated beneath the submucosa. The fact that reflexes play a part in the secretion of intestinal juice may be gathered from the close dependency of this process upon extraneous stimuli.² Thus, a dog which had not been fed for a period of about 24 hours showed a flow within 15 minutes after the ingestion of food; moreover, this flow reached its maximum in about 3 hours, *i.e.*, at a time when the pancreatic juice was produced most copiously. But since the intestinal secretion does not cease after the intestine has been completely isolated from the central nervous system by the division of the vagi and sympathetic nerves, some other agent must be at work, presumably in the form of a secretagogue. Although the nature and place of origin of this hormone have not been made out with any degree of definiteness, Delezenne and Frouin³ have proved that the injection of secretin into the blood stream of animals provided with an intestinal fistula gives rise to a copious flow of this juice. It seems, therefore, that this chemical messenger acts simultaneously upon three organs, namely, upon the pancreas, liver and glands of Lieberkühn, insuring thereby a concerted action of these secretions upon the acid gastric chyme. But certain evidence is also at hand to show that some other chemical agent is liberated in the lower part of the small intestine, synchronously with the intestinal juice. The nature of this hormone is not known.

¹ Weinland, Zeitschr. für biol. Chemie, xlvii, 1905, 279.

² Bayliss and Starling, Ergebn. der Physiol., 1906.

³ Proc. Soc. Biol., lvi, 1906, 319.

SECTION XXV

THE INTERNAL SECRETIONS

CHAPTER LXXXI

THE THYROID AND PARATHYROID BODIES. THE THYMUS, LIVER, AND PANCREAS

General Discussion.¹—The beginning of the scientific study of the ductless glands dates from 1849, when Berthold² showed that the testicles produce an internal agent which is transferred by them directly into the blood-stream. He proved his point by removing these organs from cocks and grafting them upon some other part of the body. Peculiarly enough, these animals "remained male in regard to voice, reproductive instinct, fighting spirit, and growth of comb and wattles." In 1855, Claude Bernard³ gave a more elaborate presentation of this subject by stating that glands may form a *sécrétion externe* by withdrawing substances from the blood, and also a *sécrétion interne* by passing their products into the blood. He illustrated this conception by referring especially to the liver which, in addition to its external secretion, the bile, also furnishes an internal agent which is directly concerned in the aggregation of glycogen and the formation of sugar. In 1889, Brown-Séquard, then 72 years of age, announced to the Société de Biologie de Paris that he had carried out upon himself a series of experiments with extract of testicle, proving that this therapy "has given him much physical strength, an invigoration of cerebral function, and a good appetite and digestion." Then followed a period of organotherapy during which practically every organ of the body was tested as to its remedial qualities in diseases supposedly produced by a deficiency of some internal secretion. Much of this material, however, is absolutely valueless, because aggrandized for purposes of commercial exploitation.

Brown-Séquard has added to the conception of Bernard the idea that certain glands secrete certain specific substances into the blood-stream, tending to produce a definite correlation of function between different organs. This interpretation of facts really forms the basis of a new function. Several years later Schiff compiled additional

¹ For references see: Biedl, *The Internal Secretary Organs*, translated by Williams, Wood & Co., 1913.

² *Archiv für Anat., Physiol. und wissenschaft. Medizin*, 1849, 42.

³ *Lçons de physiol. exper.*, Paris, 1855.

data pertaining to the effects following the removal of the thyroid bodies which were based in the main on the clinical observations of J. L. and A. Reverdin and Kocher on post-operative myxedema. Somewhat later Glover, Schäfer (1895), Cybulski (1895), Biedl (1898) and Dreyer (1899) studied the action of suprarenal extract upon the cardio-vascular system. In all these instances, it was shown that our body contains certain aggregates of cells which possess an altruistic function, because they supply the organism as a whole with substances having to do with its general welfare. The medium through which these organs are able to exert this influence, is the blood or more particularly the blood plasma.

Classification of the Internal Secretions.—In 1902, Bayliss and Starling showed that a flow of pancreatic juice may be evoked by means of some agent derived from the mucous membrane of the duodenum. To this substance these investigators applied the name of secretin. At about the same time Starling and Claypon demonstrated the existence of a similar stimulant in the female generative organs which induces a growth of the mammary glands. Starling, therefore, proposed to apply to all these chemical agents or messengers the name of "hormone," from the Greek *δρμάω*, to stir up or excite. But inasmuch as some of these cellular products may also retard a function, Schäfer¹ advises to include all of them under the general term of autacoid substances, from the Greek *ἄκος*, a remedy and *αὐτός*, natural. Thus, an autacoid represents any drug-like principle which is produced in the internal secreting tissues and organs. In accordance with their action, these substances may then be grouped as hormones or chalones (Greek *χαλᾶω*, to make slack). The former are excitatory and the latter inhibitory in their nature.

In most instances these internal agents are as yet wholly unknown to us chemically, and their presence can only be detected in an experimental way. In some cases, however, they have been isolated, and have been dealt with as definite chemical entities. Carbon dioxid is a substance of this kind, because it plays the part of a hormone in stimulating the respiratory center whenever produced in excess. Another one is adrenalin, a crystalline body obtained from the adrenal glands by Takamine.² It constricts the blood-vessels and raises the blood pressure. As a third might be mentioned hydrochloric acid, because it liberates secretin and as a fourth, idiothyryn which exerts a peculiar action upon the neuro-muscular mechanism. By far the greatest number of these autacoids, however, are of unknown composition and their presence can only be proved physiologically, for example, by injecting the extracts of the tissues in which they are supposed to exist into the blood-stream.

Starling emphasizes the fact that hormones belong to the crystalloids rather than to the colloids. Consequently, they are relatively

¹ Intern. Congress of Med., 1913.

² Therap. Gazette, xvi, 1901, 221.

stable substances and may be subjected to ordinary degrees of heat without losing their function, a fact which sharply differentiates them from the ferments and enzymes. To be sure, both these agents are cellular products, but while the autacoids are destructible and their function is restricted to the domain of the body, the enzymes are not limited in this way. Moreover, they are resistant, and are not changed during the processes evoked by them.

Any other classification of the autacoids meets with the difficulty that they act upon specific groups of cells and that the effect produced by them is usually rather vague in character. Thus, while the action of adrenin is quite obvious, other internal secretions, for example, those of the thyroids and thymus, possess a general metabolic function which it is difficult to analyze. Gley,¹ however, suggests the following classification:

(a) Nutritive	{	Glycose, liver,
Fat, intestinal mucosa,
Albumins of blood, intestinal mucosa and blood.									
(b) Harmozones	{	<table border="0"> <tr> <td style="vertical-align: top;">1. Substances effecting nutritive changes</td> <td style="vertical-align: top;">{</td> <td style="vertical-align: top;">sugar metabolism, pancreas,
sugar mobilization, adrenals,</td> </tr> <tr> <td style="vertical-align: top;">2. Substances helping to maintain int. medium</td> <td style="vertical-align: top;">{</td> <td style="vertical-align: top;">antithrombin, liver,</td> </tr> <tr> <td style="vertical-align: top;">3. Morphogenetic</td> <td style="vertical-align: top;">{</td> <td style="vertical-align: top;">testicles,
ovaries,
thyroid,
hypophysis,
thymus.</td> </tr> </table>	1. Substances effecting nutritive changes	{	sugar metabolism, pancreas,
sugar mobilization, adrenals,	2. Substances helping to maintain int. medium	{	antithrombin, liver,	3. Morphogenetic	{	testicles,
ovaries,
thyroid,
hypophysis,
thymus.
1. Substances effecting nutritive changes	{	sugar metabolism, pancreas,
sugar mobilization, adrenals,									
2. Substances helping to maintain int. medium	{	antithrombin, liver,									
3. Morphogenetic	{	testicles,
ovaries,
thyroid,
hypophysis,
thymus.									
(c) Hormones	{	<table border="0"> <tr> <td style="vertical-align: top;">Chemical</td> <td style="vertical-align: top;">{</td> <td style="vertical-align: top;">activating the trypsin, spleen,
catabolic, thyroid,</td> </tr> <tr> <td style="vertical-align: top;">Physiological</td> <td style="vertical-align: top;">{</td> <td style="vertical-align: top;">secretin, duodenum
adrenin, adrenals,
galactagogue, placenta.</td> </tr> </table>	Chemical	{	activating the trypsin, spleen,
catabolic, thyroid,	Physiological	{	secretin, duodenum
adrenin, adrenals,
galactagogue, placenta.			
Chemical	{	activating the trypsin, spleen,
catabolic, thyroid,									
Physiological	{	secretin, duodenum
adrenin, adrenals,
galactagogue, placenta.									
(d) Parhormones	{	Carbon dioxide, muscles and glands,
Urea, liver.									

An inspection of this table must show immediately that this classification is by no means sufficiently embracing to include all of the internal secretions in their proper relation to one another and hence, it may be permissible to arrange them in accordance with their location rather than their function. In the first place, it is to be noted that these secretions originate in the so-called endocrine organs (Greek *ἔνδον* within, and *κρίνω* to separate), including the thyroids, parathyroids, thymus, duodenum, liver, pancreas, adrenals, pineal gland, pituitary body, placenta, choroid plexus, and the testes and ovaries. Every one of these glands presents at least three of the characteristics ordinarily assigned to an internal secretory structure, namely: (a) the cells composing them are usually arranged in the form of acini, and embrace a certain amount of granular and other material from which the secretion

¹ The Internal Secretions, translated by Fishberg, Höber, New York, 1917.

may be derived. Furthermore, while not in possession of a true duct, they lie in close relation with definite efferent and afferent blood-vessels and lymphatic channels, (b) their product can be isolated chemically from their venous blood or lymph, (c) their substance or the blood or lymph returned from them, may be shown to possess a specific physiological action, and (d) the removal of the organ is followed by a loss of a definite function which is absolutely essential to the health and very existence of the animal.

A. THE THYROID AND PARATHYROID BODIES

Position and Structure of the Thyroid Gland.—In the cat, dog and man, the thyroid gland (Greek: *thyreos*, shield) consists of a right and left lobe which are connected with one another by a bridge or isthmus of the same tissue extending transversely across the trachea. These lobes are nearly equal in size, and measure about 5 cm. in length.

FIG. 503.

FIG. 503.—DIAGRAM SHOWING THE POSITION OF THE THYROID GLAND.
TC, thyroid cartilage; TG, thyroid gland; T, Trachea. The parathyroids are indicated in black.

FIG. 504.

FIG. 504.—DIAGRAMMATIC REPRESENTATION OF THE STRUCTURE OF HUMAN THYROID

Their combined weight amounts to 30 or 40 grams, but these figures are only approximate, because the vascularity of this organ is subject to considerable fluctuations. It is generally larger in females, and increases in size during the menstrual period. During adult life it shows a proportion to the weight of the body of 1:1800 and during infancy a proportion of 1:250; hence, it is much larger during the latter period.

The thyroid is developed from an outgrowth of the primitive pharynx and is, therefore, of hypoplastic origin. It is enveloped by a layer of dense areolar tissue which also subdivides its substance into small lobules of irregular size. Its tissue is composed of a large number

of vesicles which are lined by a single row of cuboidal or columnar epithelium, and contain a peculiar colloid materia¹. The size and shape of these vesicles differ greatly; some of them attaining a diameter of 1.0 mm. Langendorff states that these acini are made up of two types of cells, because while some of them appear to have reached adult size and to be actively secreting, others seem to be held in reserve until called upon to take the places of those torn away and discharged in the secretion.

The thyroid is a very vascular organ, receiving 560 c.c. of blood per 100 grams of substance in the course of a minute.¹ Its five supply channels are the right and left superior and inferior thyroid arteries, branches of the external carotid, and the thyroidea ima, which ascends upon the trachea and is a branch of the subclavian arteries. Each lobe is drained by three collecting channels, namely the superior, middle and inferior thyroid veins. This gland is also equipped with an intricate system of lymphatics which, however, do not communicate directly with the colloid vesicles. Its nerve supply is derived from the superior and inferior laryngeal nerves.

Position and Structure of the Parathyroid Glands.—The parathyroids² usually present themselves as four small rounded masses embedded in the substance of the thyroid. They are oval in shape, measuring about 6 mm. in length and 3 to 4 mm. in breadth, and their combined weight rarely exceeds 0.10 gram.³ One pair of them is usually found near the level of the lower border of the cricoid cartilage, between the wall of the esophagus and the lateral mass of the thyroid, while the second is situated as a rule opposite the third or fourth ring of the trachea in or near the lower pole of each lobe.⁴ Accessory parathyroids are encountered at times along the trachea and even in the cavity of the thorax.

The cells composing these bodies are epithelial in character and are arranged in palisade-like columns which are connected with one another by unusually vascular connective tissue. In many cases this tissue is so well developed that the entire gland appears to be subdivided into many smaller lobules. Its parenchyma is made up, on the one hand, of large polygonal chief cells, the cytoplasm of which does not stain well, and, on the other, of cells possessing a delicate, granulated interior which stains intensely with eosin and other acid dyes. The parathyroids may also contain follicles which are filled with a colloidal material similar to that occupying the vesicles of the thyroid.

Extirpation of the Thyroid and Parathyroids.—It was formerly believed that the thyroid regulates the blood-supply of the brain

¹ Tschuetsky, Pflüger's Archiv, xcvi, 1903, 210.

² Discovered by Sandstrom, Upsala Läkarefor. Förh., xv, 1880, and described by Kohn, Archiv für mikr. Anat., xlv, 1895.

³ Thomson, The Thyroids and parathyroids throughout vertebrates, Phil. transact., Roy. Soc., 1911.

⁴ Fischer, Archiv für Anat., 1911.

(Cyon), this view being based upon the fact that it is placed directly in the path of the cerebral vessels and contains at times an astoundingly large amount of blood.¹ The latter peculiarity, in particular, led Tiedemann to assume that it is a blood-forming organ. Its real nature, however, was not detected until the year 1856, when Schiff² proved that its total removal induces certain pathological conditions which invariably prove fatal in the course of three to four weeks. In spite of these perfectly definite results, the removal of this organ was resorted to a number of times in subsequent years for the relief of those serious respiratory difficulties which are usually associated with goiter. In all these cases, this surgical procedure was followed by very alarming symptoms which presented themselves chiefly as disorders in nutrition and a general muscular weakness, tremors and spasms.³ In 1884, Schiff operated upon a second series of sixty dogs of which fifty-nine died within three weeks. This study drew renewed attention to this organ, and spirited efforts were made henceforth to unravel its function. Thus, it was soon discovered that the serious symptoms following its total extirpation, could be prevented by permitting a portion of, say, its lower extremity, to remain in the body.⁴ Likewise, it was shown that the transplantation of the thyroid to some other part of the body, such as the peritoneal cavity, protects the animal against the consequences of thyroidectomy. The healing in of these transplanted segments of the gland proceeds very quickly in thyroidectomized animals so that their vascularization is practically completed at the end of the third week. In the normal animal, on the other hand, these transplants do not grow well and do not attain this stage in less than eight weeks.⁵ Lastly, Vassale⁶ proved that the alarming effects of thyroidectomy may also be obviated by the feeding of thyroid substance or the injection of thyroid extract. The conclusion to be derived from experiments of this kind is that the thyroid furnishes an agent which is absolutely essential to life.

The Symptoms Following Thyroidectomy.—The effects of extirpation of the thyroid and parathyroids differ in different animals, obviously because these structures vary in their size and position. In the herbivora, for example, the parathyroids generally lie outside the substance of the thyroid, while other animals are in possession of accessory parathyroids which are scattered as small globular masses along the trachea. In the fishes, these bodies are represented by small patches of tissue of about the size of the head of a pin which are situated

¹ Swale Vincent, *Ergebn. der Physiol.*, ix, 1911.

² *Unters. über Zuckerbildung*, Würzburg, 1859. Previous to this time we have the experiments of Astley Cooper, Rapp and Bardeleben which, however, led to no definite results.

³ Reverdin (*Rev. méd. de la Suisse romande*, 1882); Kocher (*Archiv für klin. Chir.*, 1883), and Billroth (*Wiener med. Presse*, 1877).

⁴ Eiselberg, *Wiener klin. Wochenschr.*, v, 1892, 81.

⁵ Salzer, *ibid.*, 1909.

⁶ *Neur. Zentralblatt*, 1891.

along the aorta and along the arches of the gills. If we confine ourselves, therefore, to the carnivora and include in this discussion the symptoms caused by the enucleation of the parathyroids, the following clinical picture is obtained.

The features are swollen and imperfectly outlined, owing to an edematous condition of the skin which in turn is caused by an accumulation of mucin in the subcutaneous connective tissue. Later on, the bloated appearance of the skin is aggravated by a certain roughness and dryness, which finds its origin in the cessation of the cutaneous secretions and eventually gives rise to a coarseness and falling out of the hairs. This infiltration also affects the mucous membranes, and eventually involves the respiratory passage and conjunctival sacs (myxedema). The animal loses weight steadily, and finally enters a condition of pronounced malnutrition, the so-called cachexia thyroprivia (strumipriva). But these purely metabolic disturbances which prove that thyroidectomy renders the animal unfit to utilize its food, are invariably associated with others, indicating a severe intoxication of the nervous system. To begin with, it is observed that the muscular contractions become clonic in their character, then tetanic and lastly, spastic. This leads to a marked muscular rigidity and contracture, and finally to a weakness as well as a motor and sensory paralysis of the entire body. As the anterior and posterior extremities become weakened and are no longer able to support the trunk, the animal is forced to assume the position usually occupied by it during sleep. The muscular tremors are gradually intensified and become more general in their character, terminating eventually in severe convulsions and death. Although the higher nerve centers appear to retain their function for a relatively long period of time, their irritability is gradually diminished, which renders the animal stupid and very apathetic. Death usually results in the course of 9 to 12 days.

Cretinism, Myxedema and Hyperthyroidism.—Keeping the character of the symptoms just cited clearly in mind, we are now in a better position to analyze the clinical pictures of cretinism, myxedema, hyperthyroidism, exophthalmic goiter, and the conditions forming the basis of Basedow's disease. In a general way, it may be said that man is subject either to a diminished or an increased function of the thyroid gland, or, in other words, to a deficient or an excessive formation of this internal secretion.

(a) *Cretinism* or infantilism is due either to an imperfect development of the thyroid gland or to its atrophy in later years. The infant so afflicted presents a dwarfed appearance, because the growth of the bones and soft parts has been checked. The abdomen is large and pendulous, while the legs are poorly formed and seem scarcely able to support the weight of the trunk. The face presents a swollen appearance and imperfectly outlined contours. The hair is coarse and scanty and the skin thick and dry. Mentally, the cretins are far behind children of the same age, in fact, their intelligence frequently borders upon imbecility and idiocy. Their movements are clumsy and unsteady. In many instances, this condition of infantile myxedema or cretinism resembles very closely true dwarfism,

and certain types of rachitis fetalis from which it must, therefore, be differentiated. This clinical picture may be cleared up in the course of a month or two by the feeding of thyroid substance or of an extract of thyroid. Growth begins again, the myxedematous symptoms disappear more or less completely, and the infant brightens up perceptibly from week to week. In our own country myxedematous cretinism is rather rare, but there are several regions in which it is endemic; for example, in Italy which reported 13,000 cases in 1883, and in Austria, Savoy, the Pyrenees, the Himalayas and the Cordilleras. Since these districts are mountainous and are formed by marine deposit of the Paleozoic, Triassic and Tertiary periods, cretinism has been etiologically referred to peculiarities of the soil and to the drinking water derived from these geological strata. That there is some truth in

FIG. 505.—CRETIN BEFORE (A) AND AFTER (B) TREATMENT WITH SHEEP'S THYROID.
(Nicholson, in *Arch. of Ped.*, June, 1900.)

this explanation is shown by the fact that the introduction of fresh water from other sources has eradicated this disease in at least some of these districts. Moreover, it is a matter of common experience among these people that the drinking of water from so-called "goiter-springs" gives rise to myxedematous symptoms within a short time, while filtered or boiled water does not.¹

(b) *Myxedema*.—The extirpation or atrophy of the thyroid gland in adults is soon followed by symptoms such as have just been described. The skin becomes thickened, swollen and dry and yields mucin when extracted with alkali. The hair becomes coarse and scanty. There is also present a general fatigue, a mental apathy, and a tendency to an abnormal deposition of fat. The nitrogen metabolism is reduced.

¹ Bircher, *Zeitschr. für exp. Path. und Ther.*, ix, 1911.

(c) *Hyperthyroidism*.—The condition of hyperthyroidism may be produced in animals either by the continued feeding of thyroid substance or by the intravenous injection of thyroid extract (rabbits). It is usually initiated by frequent attacks of tachycardia to which are added disorders of digestion and metabolism, such as diarrhea, intestinal hemorrhage, emaciation, polyuria and glycosuria. A few cases are also on record of persons who have taken excessive amounts of thyroid for the relief of obesity and other disorders. Thus, one person ingested in the course of five weeks nearly 1000 tablets of thyroid substance of about 0.3 gram each and developed, in addition to the symptoms just mentioned, an extreme irritability of the nervous system, psychic exultation, sleeplessness and trembling of the muscles.¹ This complex of symptoms corresponds almost precisely with that presented by persons suffering from *Basedow's disease* or, as it is now more commonly called, *Graves' disease*. In 1840, Basedow showed that the combination

FIG. 506.—EXOPHTHALMIC GOITER.

The patient shows a goiter of moderate size; great exophthalmos, smooth forehead, and abnormal expression. (*MacCallum*.)

of exophthalmos, goiter and tachycardia forms a syndrome of a not infrequent clinical condition which, in general, is just the reverse of that noted in thyreopriva, hypothyroidism or diminished thyroid function. The heart is very rapid and often irregular; the temperature is usually a degree or two above normal; the thyroid is generally somewhat enlarged; while the eyes, owing to the wide open condition of the eyelids, are very prominent and staring. To these three fundamental symptoms, others have been added in the course of more recent years, the combined clinical picture being that of *Graves' disease*. Among the secondary conditions might be mentioned an increased appetite and metabolism, insomnia, restlessness, intensified sensations, mental excitement accompanied by hallucinations, muscular tremors, anemia and loss of weight.

The etiological connection of *Graves' disease* with a hyperactivity of the

¹ The therapeutics of preparations containing the active principles of the internal secretions, is discussed in Harrower's "Practical Hormone Therapy," Höber, New York, 1914.

thyroid and a flooding of the system with an excessive amount of this secretion, is well illustrated by the fact that the partial extirpation of this organ gives rise to an almost immediate amelioration of these symptoms. In fact, in many cases it suffices to reduce the vascularity of this organ by the ligation of one of its arteries. Kocher states that these operative measures resulted in 76 per cent. of his cases in a complete cure and in another 14 per cent. in a decided improvement. The mortality which amounts to about 3 per cent., is referable chiefly to erroneous diagnosis. Simple hyperthyrosis is characterized by a slight swelling of this gland, *i.e.*, by a latent increase in its size and a few of the milder symptoms enumerated above. It occurs most frequently in young women, and is temporary in its nature.

The Nature of the Active Principle of the Thyroid.—Much uncertainty still prevails regarding the nature of the active agent contained in the secretion of this gland, although it seems established that it is derived from the colloid material of its vesicles. In this connection, it is of interest to note that a substance has been isolated from thyroid tissue by Baumann,¹ to which he has given the name of iodothyron or thyroindin. It contains as much as 9.3 per cent. of its dry weight as iodine. While the action of this substance has not been definitely ascertained, it seems certain that it is at least closely associated with the activity of this gland. This is shown by the fact that it is always present in normal glands and that the minimum amount of iodine necessary to maintain the usual histological picture of thyroid tissue, does not fluctuate materially in any given species. Moreover, in cases of hyperplasia the iodine content is invariably below the minimum value of 0.1 per cent. of the dried gland; in fact, no demonstrable quantities of this substance are ever present in extreme conditions of goiter. Very beneficial results have been obtained with this substance in the treatment of myxedema and goiter. Hunt² furnishes the following interesting analyses:

Thyroid of	Per cent. of iodine
Children.....	None
Maltese kid.....	None
Guinea-pig.....	0.05
Dog.....	0.06
Cat.....	0.08
Sheep.....	0.17
Beef.....	0.25
Hog.....	0.33
Human.....	0.23
Human in goiter.....	0.04

A similar but less complex body has recently been isolated by Kendall³ which he calls thyro-oxy-indol or thyroxin and to which he gives the formula: $C_{11}H_{10}O_3NI_3$. It is claimed that this substance exerts as powerful an influence upon cretinism and myxedema as desiccated thyroid. Thus, it may be concluded that the active principle of this internal secretion is an iodine-containing hormone, the

¹ Zeitschr. für physiol. Chemie, xxi, 1896, 481.

² Studies on Thyroid, Bull. Hygienic Lab., Washington, 1909, No. 47.

³ Am. Jour. of Physiol., Proc., xlv, 1918.

efficacy of which does not depend so much upon the iodine as upon the character of its combination with other substances. But since organic iodine complexes, such as iodine-protein, are inactive, the chief factor to be determined is how much active iodine-containing material can actually be liberated from the inactive iodine substance of the gland.

In order to prove that such an elaboration actually takes place, Rogoff and Marine¹ have followed the method of Gudernatch² and have exposed tadpoles to the influence of iodine-free and hydrolized sheep thyroid, containing varying amounts of available iodine. In the latter case, their growth was retarded, while their differentiation took place at a much faster rate. The rapidity and decisiveness with which these changes are effected, may be employed as a means of determining the intensity of the evolution of the active iodine-containing substance.

A chemical test of even greater delicacy is the nitrile reaction described by Hunt.³ If so little as 0.1 mg. of dried thyroid substance per gram of body-weight is fed to a white mouse each day for 10 consecutive days, this animal will survive as much as 10 times the amount of acetonitrile which would prove fatal to any other mouse not having received this treatment.

It is also of interest to note that the thyroid possesses marked storative qualities for iodine. Thus, if iodine is administered to animals with actively hyperplastic thyroids, this substance is rapidly stored in this gland and gives rise to definite histological changes, constituting the so-called colloid goiter. Moreover, the greatest storative power is possessed by those glands which are most hyperplastic and contain, to begin with, the smallest amount of iodine. It matters little whether the iodine is administered at this time intravenously in the form of a salt or is perfused through the excised gland.

The Function of the Thyroid and Parathyroids.—It has been noted above that the extirpation of the thyroid of carnivorous animals proves fatal almost without exception, but does not seriously inconvenience the herbivora. Whatever deviations from this general rule may have been observed, they are due in all probability to peculiarities in the distribution of the parathyroid bodies. Inasmuch as these structures were not recognized as an anatomical entity until late during the period of thyroid experimentation, many of these symptoms have undoubtedly been ascribed to the loss of this organ, although actually caused by the loss of the parathyroids. Besides, since the latter also appear in the form of accessory masses along the trachea, they may have escaped detection altogether. It need not surprise us, therefore, to find that the clinical picture following the removal of the thyroid and parathyroids, remained incomplete for some time after the beginning of this kind of experimentation.

Very shortly after the discovery of the parathyroids, Gley and others proved that the symptoms following the extirpation of the thy-

¹ Jour. of Pharm. and Exp. Therapeutics, ix, 1916, 57 and x, 1917, 99.

² Archiv für Entw. Mech. der Organe, xxxv, 1913, 457; also see: Graham, Jour. Exp. Med., xxiv, 1916, 345.

³ Jour. of Biol. Chem., 1, 1905, 33.

roid, are markedly different from those produced by the removal of the parathyroids. This general fact becomes apparent immediately if the symptoms enumerated above are subjected to a re-examination. It will then be noted that they arrange themselves in two groups, one of which is characterized by disorders of metabolism, such as malnutrition and cachexia, and the other, by defects of nervous function, such as muscular tremors and tetany. Recent investigations have fully confirmed this deduction so that it may be regarded as certain that thyroidectomy gives rise to a state of malnutrition, terminating in the condition of *cachexia thyreopriva*, while parathyroidectomy results in muscular tremors and spasms, forming the clinical picture of *tetania parathyreopriva*. Consequently, the combination of these two complexes of symptoms cannot be due to an overlapping of the functions of these two types of tissue, but must be caused by their simultaneous destruction or atrophy.

While no definite statements can be made at this time regarding the manner in which the thyroid exerts its peculiar metabolic action, it may be surmised that it develops a specific hormone which facilitates the chemical reductions in other tissues, chief among which is the nervous tissue. First of all, this agent increases the total metabolism, as is evinced by a greater excretion of nitrogen, carbon dioxide and phosphoric acid, and a greater consumption of oxygen. Upon this fact rests the therapeutic value of thyroid feeding in obesity, but since in this case the difficulty does not lie in the protein metabolism, thyroid feeding as a remedial measure against adiposity in the absence of an actual inactivity of the thyroid is a dangerous procedure. It may produce organic defects of the heart and other pathological lesions. In this connection it should also be noted that the feeding of animals with excessive amounts of meat may give rise to goiter and rickets, and that this outcome may be prevented by the simultaneous ingestion of milk, bread and bones. No definite explanation can be offered for the hypertrophy and hyperplasia of the thyroid occurring during the menstrual period and pregnancy. It cannot be doubted, however, that it indicates a close functional correlation between the different endocrine organs, and offers a plausible explanation for the peculiar metabolic and nervous symptoms exhibited by women during these periods.

The picture of tetany following the removal of the parathyroids, is very similar to that obtained in infantile tetany, the convulsions incited by gastro-intestinal disorders, eclampsia, and other conditions. It consists in a gradually increasing stiffness or rigor of the entire body, trembling, clonic and tonic spasms of the muscles, as well as a loss of muscular coördination and strength. The body-temperature rises, the frequency of the heart and respiration is increased, whereas weight is lost rapidly. This tetany may be mitigated or even abolished by the administration of sodium bicarbonate, alkalies, calcium salts¹ or

¹ Macallum and Voegtlin, Johns Hopkins Univ. Bull., 1908.

extracts of parathyroid tissue. While the exact significance of the symptoms just enumerated is not known, it appears that this tetany is the outcome of some profound metabolic change resulting in an intoxication. In other words, in the absence of this gland certain toxic substances escape reduction, and finally attack the tissues. This explanation finds substantiation in the experiments of Macallum,¹ which show that bleeding and infusion of saline solution causes the tetany to disappear, and that the injection of the blood-serum of animals in tetany produces these symptoms in other animals.

The specific hypothesis suggested by these experiments, is that the parathyroids possess the power of detoxication by preventing the accumulation of certain products of metabolism. This conclusion, however, is not fully justified, because it may also be true that these poisons are not formed in the normal body and develop only in the absence of the parathyroids. More recently, Paton² has brought forth the hypothesis that this gland regulates the metabolism of guanidin and thereby exerts a controlling influence upon the activity of the muscles. Upon its removal, the guanidin accumulates and gives rise to a fatal tetany. This contention finds support in the fact that the guanidin compounds in the blood and urine are markedly increased after parathyroidectomy and are also present in excessive amounts in the urine of children suffering from idiopathic tetany. Furthermore, it is possible to evoke the symptoms of parathyreopriva by the injection of salts of guanidin.

B. THE THYMUS GLAND

Position and Structure of the Thymus.—This glandular mass is situated in the anterosuperior recess of the mediastinal space, and covers the great vessels. By origin it is a bilateral organ, consisting of a right and left lobe with corresponding prolongations upward. This division is also in evidence in the adult organ, because although they overlap, its two portions may be separated from one another without much difficulty by following the line of the intervening connective tissue. The size of this organ differs greatly in accordance with the age of the individual. In infants, for example, its average weight is 12 grams, at puberty 35 grams, at sixty years less than 15 grams, and at seventy years less than 6 grams.³ When fully developed, it extends across the upper portion of the pericardial sac and reaches upward very nearly to the thyroid gland.

It is invested by a thin capsule of areolar tissue which also divides its substance into lobules. The different follicles entering into the formation of the latter, are made up of a central portion or medulla and

¹ Jour. Exp. Med., xi, 1909, 118, also: Jour. of Pharm. and Exp. Therap., ii, 1911, 421.

² Quart. Jour. of Exp. Physiol., x, 1917, 203.

³ Hammar, Archiv für Anat., 1906.

an external portion or cortex. The medulla presents itself as a coarse network of connective tissue in which are embedded lymphoid cells and the concentric corpuscles of Hassall. The latter are of endodermic origin, and have been formed from an outgrowth of the third pharyngeal cleft. The former, on the other hand, appear to be of mesodermic origin. The cortex is made up of a similar reticulum of connective tissue, the different nodules of which contain numerous lymphoid cells. Although derived from epithelial tissue, the cortical substance eventually acquires the general characteristics of a lymphatic gland, but this transformation is not complete, because it contains a much larger amount of nuclear material than the ordinary glands of this type. The blood-supply of the thymus is derived from the internal mammary, inferior and superior thyroid, subclavian and carotid arteries.

The Function of the Thymus.—While no absolutely definite statements can be made at this time regarding the function of this gland, it is obvious that it exercises a metabolic influence which attains its greatest importance at about the time of maturation. In support of this view might be cited the involution of this organ after puberty, and secondly, the fact that its removal gives rise to a more rapid development of the testes.¹ Correspondingly, the removal of the latter (castration) delays the atrophy of the former.² It is surmised that this close relationship of the aforesaid organs is brought about wholly by chemical means, because even pieces of the thymus of rabbits, when transplanted to other regions of the body, are affected in precisely the same way by castration and sexual stimulation.³

In accordance with Klose and Vogt⁴ it has usually been supposed that the thymus is essential to life and that its complete removal proves fatal to young animals within a very short time. While these results have not been substantiated by the work of Pappenheim, Howland and Vincent,⁵ it appears that thymectomy nevertheless produces certain metabolic disturbances, chief among which are a retardation of the growth of the bones, mental deterioration, and a tendency to adiposity. In connection with this point, attention should be called to the experiments of Gudernatsch which have shown that the feeding of extract of thymus to young tadpoles stimulates their growth, but retards their differentiation or metamorphosis. Some authors, in fact, recognize a condition of hyperthymusism which may be a complicating factor in Graves' disease.

C. THE LIVER

The Internal Secretory Power of the Liver.—The carbohydrates are absorbed in largest part through the intestinal radicles of the portal

¹ Paton, *Jour. of Physiol.*, xxxii, 1905, 28, and xlii, 1911, 267.

² Goodall, *Jour. of Physiol.*, xxxii, 1905, 191, and Pappenheimer, *Jour. Exp. Med.*, xix, 1914, 319.

³ Marine and Manley, *Jour. Lab. Clin. Med.*, iii, 1917, 48.

⁴ Klinik and Biol. der Thymusdr. Tübingen, 1910.

⁵ *Ergebn. der Physiol.*, 1911.

vein. On reaching the liver, some of the glucose, levulose, and galactose is taken up by the hepatic cells, and is deposited here in the form of a colloidal polysaccharide, known as glycogen. Consequently, one of the functions of this organ is to store and to hold in reserve a certain surplus amount of carbohydrate material until needed by the other tissues. But, since the muscles contain almost as much glycogen as the liver, the latter cannot be said to be the only place in which this substance is deposited. At all events, the liver is constantly called upon to release some of this glycogen and more particularly during the periods intervening between meals, when practically no sugar is absorbed. Lastly, this organ possesses the power of forming dextrose from protein material and even from many partially oxidized products of other tissues. This synthesis of glycogen, as well as the reconversion of this substance into sugar, must be effected by means of a special intrahepatic principle. Consequently, it may be said that this organ furnishes an internal secretory product which has to do with the metabolism of the carbohydrates.

D. THE PANCREAS

The Removal of the Pancreas.—Inasmuch as the general physiological anatomy of the pancreas has been discussed at some length in connection with its external secretion, it may suffice at this time to state that this organ also contains numerous colonies of cells which have been named, after their discoverer, the islands of Langerhans (1869). These groups of cells are tugged away in between the different acini and are composed of polygonal cells possessing poorly defined boundaries, large round nuclei, and relatively few and small granules. They are copiously supplied with blood from an interstitial system of capillaries. Bensley¹ has proved by the method of intravital staining that these structures are permanent and should not be regarded as developing reserve cells of the acini.

It was Cl. Bernard² who first called attention to the fact that the occlusion of the duct of Wirsung produces a complete atrophy of the acini of the pancreas, but does not destroy the islets of Langerhans. In 1889, Mering and Minkowski³ proved that the total extirpation of this organ gives rise not only to digestive disorders, owing to the loss of the pancreatic juice, but also to a complex of symptoms commonly associated with the disease, called diabetes mellitus. The animal shows a hyperglycemia, glycosuria, polyuria, polyphagia, a loss of weight, an abnormal thirst and hunger, emaciation and muscular weakness. This disease terminates fatally in the course of two to four weeks. Contrary to the effect of total extirpation, the removal

¹ Harvey Lectures, New York, x, 1915.

² Sebolew, Virchow's Archiv, clxviii, 1902, 91, and Homans, Journ. of Med. Research, 1914.

³ Archiv für exp. Path. und Pharm., xxi, 1893, 85.

of only a part of this organ does not produce these symptoms, nor do they appear if a portion of its tissue is transplanted. The latter procedure usually consists in grafting its processus uncinatus and corresponding blood-vessels under the skin of the abdomen. It has also been established that the ligation of the ducts of the pancreas does not produce a permanent glycosuria, but only those symptoms which are commonly associated with a loss of the pancreatic juice.

The Function of the Internal Secretion of the Pancreas.—The fact to be derived from the preceding data, is that, in addition to its digestive juice, the pancreas also produces an internal secretion which is absolutely essential to the life of the animal. While the evidence is not absolutely conclusive, it is surmised that this internal secretion arises in the cells of the islets of Langerhans. This assumption is strengthened somewhat by the statements of Opie¹ and others that these cells show signs of hyaline degeneration and atrophy in persons who have died of diabetes mellitus. The correctness of this observation, however, has recently been questioned.² Nothing definite is known regarding the cause of this disease, although it is supposed that it develops in consequence of a disturbance of the carbohydrate metabolism. Regarded from a very general standpoint, the conditions leading to glycosuria, may be classified under the following headings:

(a) *Alimentary*; too copious an absorption of sugar is frequently followed by a temporary excretion of this substance in the urine. This condition is known as alimentary or physiological glycosuria. It subsides as soon as the body has succeeded in ridding itself of the excessive amounts of sugar absorbed.

(b) *Pancreatic*; a disorder in the internal secretory power of the pancreas is the cause of this form of glycosuria.

(c) *Hepatic*; the cells of the liver do not exercise their storative functions properly, and allow too large an amount of sugar to escape into the blood.

(d) *Oxidative*; the cells of the tissues are unable to oxidize the sugar, because they lack the agent which is required to accomplish this reduction. The latter may be conveyed to them from the pancreas or may be a product of their own.

(e) *Renal*; the cells of the kidney have lost their relative impermeability and allow the sugar of the blood to pass more readily through them.

Since in the present instance we are solely concerned with the pancreatic type of diabetes, this problem may be restricted in the following way: The pancreas furnishes an active principle, possibly an enzyme, which aids in the hydrolysis or oxidation of the sugar in the tissues. In the absence of this agent, this process remains incomplete and the sugar escapes into the urine. In this case, therefore, the internal secretion of the pancreas acts in the manner of a hormone, *i.e.*, as a stimulus to cellular activity. Another view is that the pancreas furnishes an active principle which regulates the sugar output of the liver. In the absence of this agent, the cells of the liver convert their glycogen too rapidly, thereby increasing the sugar content of the blood and producing a hyperglycemia which is soon followed by a

¹ Jour. Exp. Med., v, 1901, 397.

² Vincent and Thompson, Jour. of Physiol., xxxiv, 1906.

glycosuria. In this case, therefore, the internal secretion of the pancreas acts as a chalone, because it checks the activities of the hepatic cells. The weight of evidence, however, seems to lie with the first theory which holds that this internal secretion facilitates the reduction of the sugar by the tissues. Thus, it has been found by Clark that the perfusion of the pancreas with solutions containing dextrose, causes this substance to be changed into some form of polysaccharide. On allowing this condensed dextrose to circulate through the tissues, it undergoes a further change into a carbohydrate which is easily utilized by these cells. Thus, it is claimed by Woodyatt¹ that sugar exists in the blood in some chemical combination which behaves like a colloid. The substance which combines with dextrose to form this compound, is closely related to the internal secretion of the pancreas.

The Internal Secretion of the Gastric and Intestinal Mucosa.—In elaboration of the preliminary experiments of Cl. Bernard, Popielski, Wertheim and Lepage, it was found by Bayliss and Starling that the mucous membrane of the duodenum contains a hormone, known as secretin, which is liberated whenever the reaction of the adjoining medium is changed to acid. Upon its absorption by the blood, this agent is carried to the pancreas, liver and intestine, where it excites a flow of the corresponding secretions. A similar hormone, called gastrin, has been isolated by Edkins from the mucous membrane of the pylorus. It causes a secretion of gastric juice.

CHAPTER LXXXII

THE ADRENAL BODIES, HYPOPHYSIS, PINEAL GLAND, TESTES AND OVARIES

E. THE ADRENAL BODIES OR SUPRARENAL CAPSULES

The Position and Structure of the Adrenals.²—These glands are situated in the epigastric region, one on each side of the spine and in the immediate vicinity of the upper pole of the kidney. They differ somewhat in their size, shape and position. The right organ is affixed to the inferior vena cava in close proximity to the orifice of the right suprarenal vein, while the left organ lies in relation with the left suprarenal vein, but does not come in actual contact with the cava.³ Their arterial supply is derived from three sources, namely, from the

¹ Jour. Am. Med. Assoc., 1915.

² The suprarenal capsules were first recognized by Bartholomeus Eustachius Sanctoseverinatus in 1563. An adequate description of them was given by Winslow in 1756. Their structural peculiarities have been dealt with by Meckel (1806), Ecker (1846), Leydig (1851) and Kölliker (1854).'

³ Ferguson, Am. Jour. of Anatomy, v, 1905.

aorta by two or three small branches, and from the phrenic and renal arteries.¹ It is also of importance to remember that each gland rests upon a ramification of sympathetic fibers which is known as the suprarenal plexus, and which communicates centrally by way of the greater and lesser splanchnic nerves (Fig. 226) with the sympathetic ganglia of the thorax and lumbar region. Peripherally, each suprarenal plexus is connected with the mesenteric and celiac ganglia of the solar plexus.

The right gland has a flattened, triangular outline, while the left is crescentic, its concavity being directed toward the neighboring kidney. In man, each gland measures about 3 cm. from side to side, 3–5 cm. from above downward and 4–6 mm. in thickness. Their weight varies between 4 and 7 grams, the left one being

FIG. 507.—DIAGRAM TO ILLUSTRATE THE POSITION OF THE ADRENAL GLANDS (RABBIT).

K, kidneys; V, ureters; RV, renal veins; RA, renal arteries; JC, inferior vena cava; A, abdominal aorta; S, adrenal glands; SV, suprarenal veins. In man, the two kidneys lie very nearly in the same horizontal plane; in fact, the right organ frequently below the left.

slightly heavier than the right. When cut into, each gland exhibits an outer *cortical* and an inner *medullary* region. The former is divided into compartments by a fibrous stroma derived from the outer fibrous investment. These spaces are occupied by numerous columns of intercommunicating cells which are roughly arranged in the form of a reticular and glomerular zone. The yellowish globules (lipoids) contained in these cells, are responsible for the peculiar yellowish-pink color of the entire gland. The medulla is pervaded by a stroma, enclosing groups of granular cells, which on treatment with chromic acid acquire a yellowish brown color. On account of their power of reducing this substance, they are commonly designated as chromophil or chromaffine cells. We also find here numerous nerve cells, some smooth muscle tissue, and large venous capillaries supported by fibrous tissue. These structural differences are in complete agreement with the development of this organ, because while the cortex is derived from that part of the mesoblast which gives rise to the mesonephros, the medulla is formed from an outgrowth of the sympathetic system. Besides, these two constituents of the adrenal body remain absolutely separate in some of the lower vertebrates, the

¹ Gerard, Jour. de l'anat. et de la physiol., 1913.

medullary substances appearing in them in the form of isolated globular masses along the course of the spinal nerves. A few separate chromaffine bodies, similar to or identical with the medulla of the adrenal gland, are also found in almost all the higher animals.

Removal of the Adrenal Glands.—The function of the suprarenal glands remained a matter of speculation until 1853, when Thomas Addison called attention to the fact that the degeneration of these bodies is associated with a disease which has since been named after him. It is almost invariably fatal and is characterized by a progressive idiopathic anemia, digestive disorders, diarrhea, muscular weakness, tremors, convulsions, apathy, and a bronzing of the skin. A few years later Brown-Séquard¹ showed that these symptoms also develop in animals after the complete removal of the adrenals. Death then results within two or three days after the operation. These results were proved to be correct by Nothnagel,² Tizzoni,³ and others. In addition, Stilling⁴ established the fact that the extirpation of only one of them does not prove fatal, but is compensated for by an enlargement of the opposite organ. The same favorable results may be obtained by leaving a piece of one organ in situ or by transplanting it elsewhere in the body. Subsequent to the unsuccessful experiments of Canalis (1887) and Imbort (1899), it was shown by Haberer⁵ and Stoerk⁶ that these glands may also be transplanted within the substance of the kidney, but only if their blood-supply is not interfered with. In like manner, Biedl⁷ succeeded in growing them outside the peritoneum. In all these cases, these transplants first exhibited an initial retrogression and necrosis which was followed after about five

FIG. 508.—VERTICAL SECTION OF CORTEX OF SUPRARENAL OF DOG. MAGNIFIED ABOUT 150 DIAMETERS.

a, Fibrous capsule; b, zona glomerulosa; c, zona fasciculata; d, zona reticularis. (Böhn and v. Davidoff.)

¹ Compt. rend., 1857.

² Zeitschr. für klin. Med., i, 1879, 77, and Allg. Med. Zeitschr., 1890.

³ Ziegler's Beiträge, 1889.

⁴ Rev. méd., 1888, and Ziegler's Beiträge, 1905.

⁵ Wiener, klin. Wochenschr., 1908.

⁶ Archiv für klin. Chir., 1908.

⁷ Pfliüger's Archiv, lxxvii, 1897.

months by an active proliferation. In this connection, it should also be mentioned that the results obtained by the feeding of extract of adrenal gland to animals whose adrenals had been removed, have not been encouraging. Moreover, in only a few cases has this type of organotherapy been of any use in relieving the symptoms of Addison's disease.

The General Function of the Adrenal Glands.—While the effects of total and partial extirpation of the adrenals clearly proved that these organs furnish an active principle which is absolutely essential to life, the nature of this internal agent was not revealed until the time of Oliver and Schäfer.¹ These investigators made an extract of this gland and injected it into the venous blood-stream. A rise in blood-pressure invariably resulted which was correctly referred by them to a constriction of the blood-vessels. Further experimentation then showed that this vasoconstrictor agent is a product of the medulla and not of the cortex of this gland. Nothing definite, however, could be learned regarding the function of the latter, although it was surmised that its loss gives rise to a decided muscular weakness (asthenia) of the skeletal muscles, coma, and convulsions. The evidence which has been presented in favor of this view, is chiefly indirect in its character and is based upon the following data:

(a) The symptoms just cited cannot be mitigated by the repeated or continuous administration of extracts of the medulla, in the form of epinephrin or adrenalin.

(b) It has been shown by Stewart that the discharge of epinephrin into the circulation ceases immediately after the removal of one adrenal body and the denervation of the other. This procedure, however, does not prove fatal to the animal.

(c) No beneficial results have been obtained so far by treating Addison's disease with adrenalin which is a product of the medulla.

(d) Those animals which are in possession of "accessory" adrenals in the form of separate chromaffin-bodies (rabbits), do not die after the removal of the adrenal glands, and

(e) It has been found that transplanted adrenals exhibit a degeneration of their medulla and a proliferation of their cortex.

It will be remembered that these animals develop no untoward symptoms. Thus, it cannot be doubted that the internal agent of the cortex is different from that of the medulla. While the former furnishes a still obscure product, the absence of which gives rise to the grave symptoms mentioned above, the latter gives rise to epinephrin.²

Epinephrin.—The extract of adrenal gland employed by Oliver and Schäfer,³ was obtained by simply lacerating and pounding the adrenal tissue in a mortar under a 0.7 per cent. solution of sodium chlorid.⁴

¹ Jour. of Physiol., xxviii, 1895, 230.

² Vincent, Endocrinology, i, 1917, 140, and Schäfer, The Endocrine Organs, London, 1916.

³ A year later Cybalski and Szymonowicz published the results of a series of independent experiments of similar nature (Pro. Acad. of Krakau, 1895).

⁴ In 1856 Vulpian isolated a substance from the adrenal gland which showed remarkable color reactions (Compt. rend., xliii, 1856).

The filtered extract was then injected intravenously, only a few drops being required to evoke a marked rise in blood pressure. Some years later Abel¹ succeeded in isolating this active agent by extracting the gland with weak acid and benzoylating it, but the substance which he obtained was not the pure active principle but a benzoylated compound of it. He designated this body as *epinephrin*. Later on Aldrich² and Takamine³ obtained its free base, and called it *adrenalin*. Since then physiological chemists have determined its constitution as:

It possesses an asymmetric carbon atom and, therefore, may be either levo- or dextro-rotatory. Both these forms have been prepared synthetically. Stolz and Dakin give its formula as $C_9H_{19}NO_3$.

Under normal conditions this agent is transferred from the medullary substances into the suprarenal vein, whence it reaches the general circulatory system by way of the inferior vena cava. The active principle thus normally diverted into the blood-stream, is known as *adrenin*. It need scarcely be mentioned that we may also employ the blood of the suprarenal vein in order to produce a rise in blood pressure, but it should be remembered that adrenin is an unstable body and decomposes very rapidly. This is the reason why the reaction produced by it cannot be long continued. Even adrenalin is an unstable and weak base, but is more stable as a dry, free base or as the hydrochlorid, in which form it may be kept for some time unless unduly exposed to the light and air. The amount of adrenin present in the gland may be estimated by colorimetry as well as by the amplitude of the circulatory reaction produced by it, *i.e.*, by physiological means.⁴ Its free base is extremely potent; as little as 0.000002 gram sufficing to evoke a marked change in the blood pressure. The suprarenals of human adults contain 1.0 per cent. of adrenin, those of the cat 0.15 per cent., and those of rabbits, dogs, and monkeys from 0.2 to 0.3 per cent. In this connection, it is also of interest to note that the parotid gland of the Jamaican toad secretes a similar principle in amounts equalling 5.0 per cent.

The Action of Epinephrin upon the Circulation.—The most characteristic action of extracts of the adrenal bodies or of the commercial preparation adrenalin is a rise in blood pressure and a slowing of the heart beat. But since these effects are usually obtained by injecting the diluted adrenalin into the venous blood-stream, a certain time must elapse before it can reach the arterial system to activate the vasocon-

¹ Bull. Johns Hopkins Univ., 1898.

² Am. Jour. of Physiol., v, 1901, 457.

³ Jour. of Pharm., lxxiii, 1901, 523.

⁴ Folin, Cannon and Denis, Jour. Biol. Chem., xiii, 1912, 477; Seidell, *ibid.*, xv, 1913, 197, and Stewart, Jour. Exp. Med., xiv, 1911, 377.

striCTOR mechanism. This is also true of adrenin, because inasmuch as the normal glands discharge their product into the suprarenal veins, it must first be carried through the heart into the arteries. With a normally active circulation this requires from 12 to 14 seconds. At the end of this period of time, the blood pressure rises rather abruptly, but declines very soon until its normal value has again been established. The amplitude of this reaction depends, of course, upon the potency and quantity of the adrenalin. Upon the heart, this agent acts in two ways, namely (a) by lessening the frequency of this organ through vagus-inhibition, and (b) by augmenting its force of contraction by a direct influence upon the cardiac musculature. Consequently, the division of the vagi nerves must augment the rise in blood pressure, because it prevents henceforth the inhibitory discharges of the center from reaching the heart. It should be emphasized, however, that the adrenalin does not stimulate the cardio-inhibitor center directly, but in an indirect way through its effect upon the blood pressure. As has been pointed out in one of the preceding chapters, a high blood pressure invariably elicits a reflex which slows the heart, its cause being resident in the distention of the arteries, chiefly of the root of the aorta.

Regarding the nature of this reaction, it may be stated that the adrenalin constricts the arteries, and especially the arterioles, thereby preventing normal amounts of arterial blood from escaping into the capillaries. Its action, therefore, is to increase the peripheral resistance by lessening the size of the arterio-capillary outlet. At this point of the vascular system two elements are present, namely the smooth muscle cells and the terminals of the vasomotor nerves. Where then is the point of attack of the adrenalin? Since this rise in blood-pressure may also be produced after the destruction of the cord and sympathetic ganglia and even after the completion of secondary degeneration of the postganglionic fibers, it cannot justly be regarded as a nervous reaction. Moreover, the evidence so far presented tends to show that it does not affect the contractile elements of the smooth muscle cells directly, but some substance interposed between the latter and the terminals of the nerve. In accordance with Langley and Elliott, it must be concluded that this structure is the myoneural junction which is composed of receptor substance, *i.e.*, of a type of neuroplasm somewhat distinct from ordinary nerve tissue. Adrenalin, therefore, acts upon the myoneural connection between the sympathetic nerve fibers and the muscle cells.

At the hand of this fact, it will now be seen that the adrenin discharged by the adrenal bodies, must exercise a similar function. It is poured out as a rule in insignificant amounts and aids in keeping the vascular system in a semi-constricted condition *i.e.*, in a state of tonus. Moreover, in consequence of definite stimuli, larger amounts may be discharged at any time which actually constrict the blood-vessels and give rise to a temporary increase in blood pressure. This

statement, however, is not intended to imply that the tonus of the vascular system depends exclusively upon the presence of adrenin in the blood-stream. Such an assertion cannot be correct, because the walls of the blood-vessels are already tonically set by virtue of the tonic-ity resident in all living cells, and all the adrenin can do is to vary their tonus. The fact that adrenin is liberated at a definite rate may be proved by applying a temporary ligature to the suprarenal vein. Very shortly after this obstruction to the venous return has been removed, the blood pressure invariably shows an abrupt rise which indicates that a certain amount of the accumulated adrenin has reached the general circulatory system. Very similar results may be obtained by temporarily blocking the inferior vena cava centrally to the orifices of the suprarenal veins. Whenever the blood is then allowed to escape from this pocket, the arterial pressure rises, again proving that this stagnated cava blood has been charged with adrenin. Under ordinary conditions, however, the amount of this "spontaneously" liberated adrenin is very small. Thus, Stewart and Rogoff¹ estimate it in cats at only 0.001 gram per minute. If this amount is added to the blood of the general circuits, it will be seen that its concentration must be diminished so as to render it practically ineffective. Actual changes in the circulation, therefore, can only occur when its discharge is increased by stimulation.

The adrenalin or adrenin introduced into the circulation, is oxidized very soon after it has performed its temporary excitatory action. This instability also accounts for its rapid disappearance from food, so that perfectly enormous doses of it must be administered by mouth before it can produce its effect upon the blood pressure. Certain substances, however, have been isolated from the amino-acids by a process of decarboxylation which, although similar in their composition to adrenalin, possess a much greater stability. Some of these form the active principle of ergot. Adrenalin applied locally to open surfaces constricts the blood-vessels and may therefore be employed as a means to stop excessive hemorrhagic oozing. When added to solutions of sodium chlorid used for purposes of infusion, it acts as a vasoconstrictor agent, thereby raising the blood pressure and producing a stimulation of the heart by establishing a much greater peripheral resistance than could be obtained with the sodium chlorid alone.

The Innervation of the Adrenal Bodies.—The activity of the adrenal glands, at least of their medullary portions, is controlled by nerve fibers which are derived from the greater splanchnic nerves. Thus, Biedl² and Dreyer³ have shown that the stimulation of this nerve, or of its distal end, gives rise to a copious discharge of adrenin which, upon reaching the distant arterial system, constricts these

¹ Jour. Exp. Med., xxiv, 1916, 709.

² Pflüger's Archiv, lxvii, 1897, 443.

³ Am. Jour. of Physiol., ii, 1899, 283.

blood-vessels and produces a second rise in pressure. Attention has already been called to the fact that the stimulation of the aforesaid nerve evokes a rise in the arterial pressure which really consists of two parts, the first elevation being caused by the direct constriction of the blood-vessels of the splanchnic organs, and the second by the constriction of the blood-vessels of the general circuits in consequence of the delayed entrance of adrenin.

The fact that the adrenal bodies may be influenced reflexly, has given rise to the assumption that this mechanism is held in reserve to be activated at irregular intervals by afferent stimuli which find their origin in different parts of the body. Even emotions are said to give rise to a discharge of adrenin which then evokes the peculiar vascular reactions and sensations usually experienced during anger and fright.¹ In continuance of this line of thought it is generally believed that the condition of hypertension, which is developed in nephritis, is the direct outcome of a continuous liberation of adrenin and that this agent, owing to its power of mobilizing sugar, must be instrumental in the production of hyperglycemia and glycosuria. All these and similar statements, endeavoring to equip the adrenals with emergency functions of this kind, should be received with scepticism, because they are still lacking a definite experimental basis. Some writers, for example, are of the opinion that emotional hyperglycemia may be produced so easily in animals that it is difficult to ascertain the normal sugar content of their blood unless precautions are taken to shield them against excitement.² Others, again, hold that a real emotional glycosuria does not exist.³ Besides, Stewart and Rogoff⁴ have not been able to demonstrate any increase in the percentage of sugar in the blood of normal cats which could justly be referred to emotional states. Nor have these authors been able to detect any difference in this respect between normal cats and cats deprived of their adrenals by enucleation or nerve-section. Accordingly, it must be concluded that the mobilization of sugar occurring during experimental hyperglycemia is not evoked by adrenin, nor is the so-called emotional hyperglycemia a common phenomenon. This diversity of opinion demands that care be exercised in attributing to the adrenal bodies an array of functions which in reality are mere conjectures.

Other Actions of Epinephrin.—Since epinephrin serves more especially as a stimulant of the sympathetic division of the autonomic nervous system (Langley), it may be conjectured that its action is a very general one, involving all the smooth muscle tissue and gland tissue ordinarily under the control of these elements. Moreover, since it acts as a general excitant of the sympathetic system, the effect

¹ Cannon, *Am. Jour. of Psych.*, xxv, 1914, 256.

² Schaffer, *Jour. Biol. Chem.*, xix, 1914, 297.

³ Ross and McGuigan, *ibid.*, xxii, 1915, 407.

⁴ *Am. Jour. of Physiol.*, xlvi, 1917, 543.

produced by it may be either an augmentation or an inhibition in accordance with the structural characteristics of the effector so affected. This also implies that the reaction thus ensuing, is practically identical with that induced by the stimulation of the sympathetic fibers themselves. As has been stated above, the action of adrenalin is made possible through the intervention of a special receptor substance. Thus, Meltzer¹ has shown that adrenalin administered intravenously, dilates the pupil, while its direct instillation into the conjunctival sac is not followed by this reaction unless the superior cervical ganglion has been removed beforehand. This agent may also be employed to determine the constrictor power of the different blood-vessels. In illustration of this statement it might be mentioned that its injection into the cerebral circulation gives a positive reaction, while its injection into the pulmonary circuit does not. The inference to be derived from these tests, is that the blood-vessels of the brain are equipped with a vasomotor mechanism, while those of the lungs are not.

Inasmuch as the smooth muscle tissue of the walls of the intestine is supplied with inhibitory fibers from the sympathetic division of the autonomic system, adrenalin must cause a loss of its tonus and a disappearance of intestinal peristalsis. A similar effect is produced by it upon the walls of the stomach, gall-bladder and urinary bladder. In the case of the pregnant uterus of the cat, it gives rise to a contraction, but to a relaxation in the non-pregnant organ. The vas deferens and seminal vesicles are contracted, while the plain musculature of the bronchioles is relaxed. It also possesses a relaxing influence upon the blood-vessels of cardiac² and striated muscle tissue.³ It stimulates the activity of the salivary and lacrimal glands.

In addition to these effects upon the neuromuscular and neuroglandular substance, adrenalin also influences the metabolism of the different food stuffs, chiefly of the carbohydrates. This deduction is based upon the fact that its administration gives rise to the condition of adrenalin-glycosuria, for the obvious reason that it interferes in some manner with the oxidation of the sugars. Its point of attack, however, has not been definitely ascertained, although it has been stated by Underhill and Closson⁴ that it activates the sympathetic fibers regulating the formation of dextrose from glycogen. Others, again, believe that it influences the liver cells directly, causing them either to discharge a more abundant amount of dextrose or to hinder them in their storage of glycogen. At all events, adrenalin mobilizes dextrose, but certainly not by evoking a greater production of sugar from proteins or fats. Consequently, the condition of adrenalin-hyperglycemia and glycosuria cannot be directly related to diabetes

¹ Am. Jour. of Physiol., ix, 1903, 252, and *ibid.*, xi, 1904, 28.

² Gunn, Quart. Jour. Exp. Physiol., vii, 1913, 75.

³ Hoskins, Gunning and Berry, Am. Jour. of Physiol., xli, 1916, 513.

⁴ *Ibid.*, xvii, 1906, 42.

mellitus, because the metabolism of the sugars is interfered with in this disease in a much more extensive manner.¹ Since the action of adrenalin seems to be concentrated upon the liver, it cannot surprise us to find that it also incites a more copious discharge of other products. Thus, Cannon² has found that the intravenous injection of this agent in amounts of 0.0001 mgr. per kilo of body weight (cats) shortens the coagulation-time of the blood. In addition, it has been shown by Cannon and Nice³ as well as by Gruber⁴ that this procedure is followed by a temporary improvement in the power of contraction of fatigued

FIG. 509.—MEDIAN SAGITTAL SECTION THROUGH PITUITARY OF MONKEY; SEMIDIAGRAMMATIC. (Herring.)

a, Optic chiasma; *b*, third ventricle; *c*, *g*, pars intermedia; *d*, epithelium of pars intermedia extending round neck of pars nervosa; *e*, pars glandularis seu epithelialis; *f*, intraglandular cleft, lying between pars glandularis (*e*) and pars intermedia (*g*); *h*, pars nervosa.

muscles, a change which, owing to the small doses employed, cannot be due to improved circulatory conditions. More recently, it has been pointed out by Hartmann and Fraser⁵ that subminimal doses of this agent give rise to a vasodilatation. It should be remembered, however, that these effects have been obtained under experimental conditions and that they do not justify the deduction that they also occur normally in consequence of the outpouring of varying amounts of adrenin.

¹ Lusk and Riche, *Arch. Int. Med.*, xiii, 1914, 673.

² *Am. Jour. of Physiol.*, xxxiv, 1914, 255.

³ *Ibid.*, xxxii, 1913, 44.

⁴ *Ibid.*, xxiii, 1914, 335, also: *Endocrinology*, iii, 1919, 145.

⁵ *Ibid.*, xlv, 1917, 353.

F. THE PITUITARY BODY OR HYPOPHYSIS CEREBRI

Position and Structure of the Hypophysis.—In human beings this structure lies at the base of the brain directly behind the optic chiasma; and occupies a niche in the sella turcica of the sphenoid bone. It appears as a reddish-gray mass of about the size of a pea which is connected with the ventricular region of the brain by a narrow stalk, called the infundibulum. The body of this gland consists of two lobes, an anterior and a posterior. They are closely approximated, the cleft-like space between them being filled with a yellowish fluid. Owing to the fact that the cells lining this space posteriorly, present several distinctive structural features and doubtlessly secrete the aforesaid fluid, they are commonly regarded as forming a special part of the pituitary which is known as the pars intermedia. Gross anatomically, however, these cells belong to the posterior lobe.

The two lobes of the hypophysis differ widely from one another in their structure, development and function. The posterior one is developed as a hollow outgrowth of that part of the embryonic brain which later on becomes the third ventricle. While this communication is obliterated in man, it remains open in certain animals. The anterior lobe first appears as an extension of the ectoderm of the buccal cavity. After the obliteration of this prolongation, the epithelium arranges itself in the form of trabeculæ which are invested by a close network of uncommonly large capillaries, and contain certain cells which are sharply differentiated from the others by their content in deeply staining granules of chromophil. Contrary to the general neuroglia-like character of the posterior lobe, the pars intermedia has the appearance of ependymal tissue. Herring¹ has called attention to the fact that these cells embrace a material which stains in the form of globular masses of colloid-like material. From this brief structural survey it may be gathered that the anterior lobe possesses the characteristics of a ductless gland which discharges its product directly into the blood-stream,² while the intermediate part discharges its secretion into the infundibular space and the cerebral ventricles. The structure of the posterior part, on the other hand, would not lead us to infer that it possesses a secretory function.

Removal of the Hypophysis.—The experiments of Horsley (1885), Dastre (1889), and Clay (1891) have shown that the total removal of the hypophysis is followed by death within a few days, the symptoms displayed by these animals being similar to those following the extirpation of the thyroid or adrenal bodies. But since this organ is very inaccessible, some of these symptoms may not be caused by the loss of the hypophysis at all, but by injuries to neighboring parts, such as the tuber cinereum with which its anterior portion lies in close contact. This possibility, however, does not seem to have played an actual

¹ Quart. Jour. of Exp. Physiol., i, 1903, 121.

² Bell, *ibid.*, xi, 1917, 77.

part, because the subsequent experiments of Caselli (1900), Gaglio (1902), Fischera (1905), Aschner (1912), Biedl (1913), and Cushing,¹ have given practically identical results. Only a few of the hypophy-sized animals survived for a longer period than two or three months, and in these it was impossible to determine whether any of the essential tissue had been left behind. It was also demonstrated in these animals that the two lobes of this organ possess different functions, the extirpation of the anterior one proving fatal immediately, while that of the posterior one did not produce decisive symptoms for some time thereafter. In the latter case, the animals usually died from some incurrent condition. Likewise, no immediate symptoms developed after the partial removal of the anterior lobe, the animals meanwhile acquiring extensive layers of fat in the omentum and retroperitoneal spaces, and gradually developing a condition very similar to infantilism.

Pituitrin.—Subsequent to the observation of Oliver and Schäfer,² that the extract of the hypophysis gives rise to a marked increase in blood pressure, a substance was isolated from the posterior lobe to which the name of pituitrin or hypophysin has been given.³ When injected into the venous blood-stream, this agent raises the arterial pressure very materially as well as for a considerable period of time. There is no doubt that this hypertension originates chiefly in a constriction of the peripheral blood-vessels, although this substance also seems to strengthen and to slow the heart beats. When compared with the action of adrenalin, it must be conceded that it produces a much more lasting although not quite so powerful effect, and that its action is exerted upon the muscle tissue directly and not upon the nervous terminals.⁴

The Function of the Posterior Lobe of the Hypophysis.—When studying the action of extracts of the entire posterior lobe, it must be remembered that the active principle here involved is a product of its glandular pars intermedia and not of its neuroglia-like posterior portion. When injected intravenously, such extracts cause the smooth muscle tissue throughout the body to contract, thereby constricting the arteries and arterioles and raising the arterial pressure. The same effect is produced upon the urinary bladder and uterus, both these organs being contracted very powerfully but more so by the first injection than by the subsequent injections.⁵ Upon this action is based the therapeutic value of pituitrin as an agent promoting the emptying of the pregnant uterus, but its application in obstetrical practice should be restricted to particular cases. It is a safe agent in the hands of only the most experienced practitioners.

¹ The Pituitary Body and Its Disorders, 1912, also see: Houssay, *La accion fis. de los extr. hipofisiarios*, Flaiban, Buenos Aires, 1918.

² *Jour. of Physiol.*, xviii, 1895, 23.

³ Engeland and Kutscher, *Zeitschr. für Biol.*, lvii, 1911, 527.

⁴ Cramer, *Quart. Jour. Exp. Physiol.*, i, 1908, 189.

⁵ Frankl-Hochwarth and Fröhlich, *Wiener klin. Wochenschr.*, 1909.

In addition, pituitrin stimulates the flow of certain secretions. Thus, it has been observed by Ott and Scott¹ that it causes a copious flow of milk from the mammary glands, if administered to pregnant or parturient cats and other animals. In woman, it gives rise to a similar effect which is initiated by a feeling of pressure and discomfort in the mammæ. At the present time, however, it cannot be stated definitely that it serves as an actual stimulant to the secreting cells, because its action may be an indirect one, effected by contracting the smooth muscle cells lining the lactiferous ducts. In addition to its action as a galactagogue, it exerts a favorable influence upon the formation of the cerebrospinal fluid and urine. In the latter case, it is still doubtful whether its diuretic influence is due to its power of augmenting the circulation or to a stimulating influence upon the renal cells.

The Function of the Anterior Lobe of the Hypophysis.—In contradistinction to the posterior lobe, extracts of the anterior lobe produce no immediate changes when injected into the blood-stream. Contrariwise, the studies of Pierre Marie² upon the disease, known as acromegaly, have proved beyond doubt that the pathogenesis of this form of gigantism is in some way connected with the hypophysis. Clinically, acromegaly presents itself as a complex of symptoms suggesting the presence of a cerebral tumor. The patient, usually an adult, complains of headache, vertigo, vomiting, failing in intelligence, somnolence, hemianopsia, and progressive amblyopia. The face becomes distorted, owing to an enlargement of the facial bones and soft parts; the lips swell; the eyelids thicken, and the lower jaw becomes very prominent. The other forms of gigantism appear early in life and are characterized by an excessive growth of certain bones, chiefly the long bones and those of the face. In all these cases, it has been ascertained that the hypophysis is very active, as is evinced by its large size and a hyperplasia of the glandular elements of the anterior lobe.³ It has also been demonstrated that this gland is rudimentary in true dwarfs.

In correlating these clinical pictures of hyper and hypopituitarism, it is made obvious by exclusion that the anterior lobe of the hypophysis produces a hormone which controls the growth of the connective tissues. In the absence of this internal secretion in young animals, their growth is checked so that they gradually pass over into a condition of infantilism. Conversely, a hyper-activity on the part of this gland gives rise to gigantism, general and local. This result may be produced either directly through the action of this hormone upon the nervous system, or indirectly through its action upon other internal glands of the metabolic type, such as the thyroid and thymus. This

¹ Therap. Gazette, xxxv, 1911, and Simpson and Hill, Am. Jour. of Physiol., xxxvi, 1915, 77.

² Brain, xii, 1890, 59, and Marie and Marinesco, Arch. de méd. exp. et d'anat. path., 1891.

³ Benda, Handb. der path. Anat. des Nervensystemes, Berlin, 1904.

conclusion is strengthened materially by the results of organotherapy. Thus, Robertson¹ has succeeded in isolating a substance which he calls tethelin. It contains nitrogen and phosphorus and exerts a stimulating influence upon the growth of mice. Favorable results have also been obtained by Schäfer² by feeding preparations of the anterior lobe to young rats. Magnus, Levy and Falta report that the

FIG. 510.—ACROMEGALY.

This man was an acromegalic giant aged thirty-five, with blindness and large tumor of the hypophysis. (*Cushing.*)

administration of extracts of the hypophysis increases the decomposition of the proteins.

G. THE PINEAL GLAND OR EPIPHYSIS CEREBRI

Position and Function of the Pineal Gland.—In man this structure lies free between the anterior corpora quadrigemina, its base being directed forward across the roof of the third ventricle. In early life it exhibits a glandular appearance and is subdivided by connective tissue septa into lobules which are made up of pale granular cells. At about the seventh year it shows signs of involution, its glandular

¹ Jour. of Biol. Chem., xxiv, 1916, 397, and Schmidt, Jour. Lab. Clin. Med., ii, 1917, 719.

² Quart. Jour. of Exp. Physiol., v, 1912, 203.

elements then being gradually displaced by connective tissue and glia tissue of a very fibrous type. Hyaline degeneration sets in, leading to the formation of calcareous concretions of calcium phosphate and calcium carbonate which constitute the so-called brain-sand.

Virchow first called attention to the fact that the pineal gland is frequently the seat of cystic growths and gliomas. The clinical picture presented by persons so afflicted is very similar to that noted in diseases of the pituitary body, with the exception that sexual infantilism is absent.¹ There may be observed an obesity and cachexia as well as certain trophic disturbances. Further than this no definite statements can be made, as is evinced, for example, by the recent papers of Horrax² and McCord.³ The first of these leads us to infer that the removal of this gland in male guinea-pigs favors the development of the sexual organs and hastens the sexual maturity and breeding power of the female. The second paper, on the other hand, informs us that the feeding of pineal gland to young guinea-pigs hastens their sexual maturity and favors their growth. These series of experiments, therefore, would lead to believe that hypo and hyperpinealism produce practically homologous results, and that the extract of this organ acts as a chalone as well as a hormone. Obviously, further investigation is urgently needed to clear up this point.

H. THE GENITAL ORGANS

The Function of the Ovaries.—Since the external and internal secretions of these organs will be dealt with in greater detail in a later chapter, the present discussion may well be restricted to the chemical interrelationship existing between these structures and others. In the first place, it should be noted that the secretion of the ovaries may produce either a local or a general effect. Thus, it is a well-known fact that castration in women is followed by regressive changes in their genitals, such as atrophy of the uterus and vagina. This fact has led to the assumption that the ovaries serve as the trophic center for these parts, but since the transplantation of these organs or the grafting of a part of their tissue in other regions of the body does not allow this condition to be developed, this control must be exercised by them with the aid of some chemical agent. This deduction is also justified by a study of the relationship existing between ovulation and menstruation, because it is entirely probable that the latter process is initiated by an active principle secreted by the cells forming the corpus luteum. Lastly, this conclusion is upheld by the disturbing general symptoms which generally follow in the wake of castration. It is a matter of common experience that a woman whose ovaries have been removed for the cure of a tumor or cystic growth, very frequently

¹ Deutsche Zeitschr. für Nervenheilkunde, 1909.

² Arch. Int. Med., 1916.

³ Proc., Am. Med. Assoc., June, 1914.

develops well-defined general symptoms of a nervous and metabolic kind. These disturbances are manifested most typically by vasomotor reactions, commonly called "hot flushes," sensations of alternating heat and cold, sweating, vertigo, muscular pains, and headache. In fact, in severe cases certain psychoneurotic conditions may arise which finally lead to mental aberrations. The contention that these symptoms are attributable to the loss of an internal secretion of the ovaries, is strikingly betrayed by the results of organotherapy. If an extract of whole ovary is administered to the castrated women, these symptoms most generally lose their intense character and are shortened in their duration; in fact, it is not at all uncommon to see them disappear altogether in consequence of this treatment. Moreover, the fact that extracts of the entire ovary are more beneficial than extracts of corpus luteum, seems to show that this general metabolic hormone is not necessarily a product of the corpus luteum or Graafian follicles. Bouin¹ refers this function to the peculiar stroma cells which he designates as the *glande interstitielle l'ovaire*.

While these local and general effects following the removal of the ovaries, are quite definite, it has not been established as yet whether the active principle of these organs acts directly or indirectly through the secretions of other ductless glands. It has previously been shown that the ovary is in functional relation with other endocrine organs, thus forming a special group which might be named the sexual glands. It is a well-known fact that Graves disease is very deleterious to pregnancy and that operations upon the pelvic organs are prone to intensify the symptoms of hyperthyroidism. Castration also increases the weight of the hypophysis, thymus, and adrenal glands.

The Function of the Testes.—It has been known for some time that the testicles furnish an internal secretion in addition to their external product, the spermatozoa. Quite aside from the claim of Brown-Séquard, that extract of testicle possesses an invigorating influence, it has been shown by Poehl² that "spermin" acts as a "physiological catalytic" and increases the action of the heart and digestive organs. Later on Zoth and Pregl³ proved by means of the ergograph that testicular extract augments the muscular power by as much as 50 per cent. and diminishes muscular fatigue. A more general influence of the testes upon the general condition of the body is evinced by the symptoms following the total removal of these organs. This procedure which is commonly known as castration or spaying, has been practised upon animals since the earliest times. In the case of the domestic animals, such as the bulls, stallions, rams and cocks, the invariable result is an insufficient development of the sexual organs and secondary sexual characteristics. Their transformation, however, is never complete, *i.e.*, castrated males never completely assume the

¹ Compt. rend., 1907, 337.

² Zeitschr. für klin. Med., 1894.

³ Pflüger's Archiv, lxii, 1896, 335.

characteristics of the opposite sex. Thus, while the ram lambs may develop horns, the further growth of the latter is arrested at an early stage. Quite similarly, the castrated cock shows an early withering of the comb and wattles. The loss of these and other secondary characteristics, however, may be prevented by removing only one testicle or by grafting one in some other part of the body.

Very similar effects have been noted in human beings. Thus, it is a well-known clinical fact that castration inhibits the growth of the prostate and actually incites retrogressive changes in this organ. In castrated dogs, this atrophy may be greatly retarded by the subcutaneous injection of testicular extract. The stories of the East also tell us that castration, when effected during the prepubescent period, gives rise to a defective development of the sexual organs which, however, involves the penis in a lesser degree than the purely glandular tissues, such as the seminal vesicles and the prostate. This difference is easily explicable upon the ground that the penis is chiefly composed of connective tissue. In these individuals, the secondary sexual characteristics are seldom fully developed, as is shown by the fact that the pelvis of eunuchs generally retains its infantile character, and that the amount of axillary and pubic hair is usually very slight. The child-like soprano character of their voice is referable to an arrested growth of the larynx. Moreover, they are prone to become phlegmatic and to develop a heavy panniculus adiposus which smoothenes their contours and gives them a feminine appearance. These observations may in a large measure be repeated by a study of hermaphroditism in animals and man, but sexual dimorphism does not always remain confined to the primary sexual characteristics but may also involve secondary ones. The "feminine" man and "masculine" woman are instances of this type of hermaphroditism, showing unisexual mechanisms but heterologous secondary characteristics.

It cannot be doubted, therefore, that the testes control the development of the sexual characteristics. This end they are able to attain by means of a chemical agent and not by nervous reflexes. In seeking the place of origin of this hormone, it is of interest to note that the ligation of the vas deferens, brings about a retrogression of the spermatogenetic elements but not of the interstitial cells of these organs. Contrary to the castrated animals, these animals show perfectly normal sexual characteristics and instincts.¹ Furthermore, Steinach² has proved that the transplantation of the testes does not destroy these tendencies and that the transplanted organ exhibits a proliferation of its interstitial cells and an atrophy of its spermatozoid cells. In this connection, it is also of interest to note that transplantations in very young animals may give rise to an almost complete reversion of the secondary sexual characteristics. Thus, the grafting of an ovary from a female rat or guinea-pig into a young castrated male of the

¹ Tandler, Wiener, klin. Wochenschr., 1908, 1910.

² Steinach, Pflüger's Archiv, cxliv, 1912, 71.

same species produced a pseudo-hermaphrodite, which presented primitive male generative organs and female secondary characteristics. In conclusion, it may therefore be stated that the internal secretion of the male generative gland is furnished by the interstitial cells of Leydig. Enclosed in the cytoplasm of these cells we find granules and peculiar crystals which impart to them the appearance of true secretory elements. These bodies may be the precursors of this internal product.

PART VIII

METABOLISM

SECTION XXVI

DIGESTION

CHAPTER LXXXIII

THE CHEMISTRY OF DIGESTION

General Consideration.—The term of assimilation as originally employed by the botanists, included all those processes which the plants must undergo in order to synthesize the inorganic substances into the organic compound starch. When employed in this general way, it embraces all those chemical and mechanical processes which lead to the reduction, absorption and assimilation of the different foodstuffs by the cells. These stages are followed by cellular dissimilation and excretion. At the present time, all these processes are generally included under the term of metabolism which is divided in turn into a process of building up, or anabolism, and a process of tearing down, or catabolism, as follows:

In the lower forms, the process of digestion is completed outside the cells, enabling them to attain their nutritive material in a fluid condition ready for assimilation. Beginning with the celenterates, on the other hand, digestion is chiefly intracellular and hence, the metabolism of the higher forms requires the presence of special organs, the purpose of which is to reduce the nutritive material sufficiently to render it dialyzable through animal membranes, and assimilable by the cells. But since the food must be reduced mechanically as well as chemically, two types of organs must really be present which severally accomplish these ends. In most instances, however, the mechan-

ical and chemical mechanisms are combined in such a way that both kinds of reductions may be had within the confines of the same organ. Obviously, the histological elements more directly concerned with them, are the striated and smooth muscle cells and the gland cells.

The food made use of by the higher animals, is heterogeneous in its character, consisting of inorganic and organic principles, and a certain amount of non-digestible and non-nutritive material, such as connective tissue and the cellulose of the plants. The predigestive procedures which man employs in preparing his food, cannot materially alter this condition, because only very few non-assimilable materials can be made available thereby. This is true of the process of cooking as well as of that of maceration. All that can be accomplished by these means is to free the nutritive principles from their non-digestible investments, and to increase the solvent action of the different digestive juices, so that they may be more readily reduced, chemically as well as mechanically. Nutritive material is consumed in the form of food, consisting of different foodstuffs. Consequently, a food is a mixture of nutritive substances, whereas a foodstuff is a single nutritive substance. The latter are grouped as water, salts, carbohydrate, fat, and protein, and may be arranged as nitrogenous and non-nitrogenous substances, as follows:

Obviously, the purpose of food is to replenish the material which has been used up by the cells during their oxidations in furnishing the energy upon which the bodily machine is run. Were this waste to continue without being balanced by an adequate intake, the animal would soon have to discontinue its activities. Moreover, since food as exemplified by meat, potatoes, milk, bread, etc., is invariably made up of several foodstuffs, it will be seen that our diet usually consists of several of the proximate principles just mentioned. In fact, no diet can be regarded as adequate for man which does not embrace all the different foodstuffs, mixed in proper proportion, to burden the body with only a minimum of labor.

Water, salts and some carbohydrates, such as dextrose, are capable of traversing the intestinal epithelium in their original form, whereas the indiffusible colloidal carbohydrates, such as starch and dextrin, must first be converted into soluble and diffusible sugar. This is also true of the fats which must first be changed into glycerin and fatty acids, and the natural proteins which must first be converted into diffusible peptones and simpler compounds. As stated above, digestion does not end here, but in addition imparts to the now diffusible end-products of the different foodstuffs a form which will enable the cells

of the tissues to utilize them. For this reason, the disaccharides, such as cane-sugar, maltose, and lactose, are first converted into monosaccharides, such as dextrose, levulose, and galactose, while the protein molecule is split up into amino-acids.

Ferments.—The word ferment was formerly applied to living organisms such as the yeast cells, which during their conversion of sugar into carbonic acid and alcohol, cause the liquid to boil up (*fervere*), owing to the evolution of this gas. For similar reasons this entire process was designated as fermentation. In recent years, however, many similar substances have been found in animal and vegetable cells, so that the term of ferment is now applied to all those complex organic bodies which are capable of inciting a chemical reaction without they themselves undergoing a quantitative or qualitative alteration. Hence, any fermentation must derive the energy evolved in the course of this process from the substances concerned in it and not from the activating agent. Besides, no direct relationship can exist between the amount of the ferment and the intensity of the reaction. This implies that even the most minute amounts of ferment are capable of inducing chemical changes in proportionately much larger quantities of reducible material, and that the addition of more ferment can only serve to quicken the reaction, and not to alter its character. A chemical change of this kind is known as a catalysis, while the agent producing it is designated as a catalyzer or catalyst. The substance acted upon by the catalyzer is termed the substrate. There are, of course, many other catalytic agents besides the ferments. Thus, potassium chromate may act as the catalyzer for the oxidation of hydriodic acid by bromic acid or spongy platinum, and may cause the spontaneous combustion of hydrogen peroxide into water and oxygen.

Until comparatively recently, ferments have been classified as organized and unorganized, or as living and dead. Among the former might be mentioned the yeast plant or *saccharomycetes*, and a large number of bacteria, and among the latter, the different active principles of the digestive juices, such as *ptyalin*, *pepsin*, *trypsin*, and others. On the one hand, therefore, we have living cells possessing a distinct organization, and, on the other, dead substances, which in most instances have not been satisfactorily isolated and are known to be present solely from the reactions incited by them. While this classification is easily understood, it is no longer tenable, because it has been shown that the yeast cell and allied living entities may be made to give up their ferments by chemical means without that the latter lose their power of inciting fermentation. In other words, it is not at all essential to the action of the ferment that it be carried by living matter, and hence, it must be considered merely as a product of cellular metabolism. Consequently, it is really as “unorganized” as the enzyme of the cells of the salivary glands or any other (Buchner 1897), and hence, the terms of ferment and enzyme are now synonymous

in their meaning. The distinction commonly made between them at the present time, is based upon their place of action. Thus, we may speak of an intracellular or endo-enzyme, when it acts in the cells in which it originated, and of an extracellular or exo-enzyme, when it acts outside its mother-cell. There is every reason to believe that the action of yeast is due to the intracellular behavior of its endo-enzyme (zymase), while, for example, saliva owes its chemical power to its extracellular exo-enzyme, ptyalin.¹

The Nature of Ferments.—Since ferments are not destroyed in the course of the processes incited by them, the medium must contain them even after the reaction has ceased. In the cells themselves they are held in an inactive form which is somewhat different from that of the active derivative. But, the fact that ferments are never present in abundant amounts is not the only difficulty met with in isolating them in a sufficiently pure state to determine their chemical nature. Many of them are very unstable and are rendered inert at 80°C., and all of them are colloidal or semi-colloidal in their nature and not easily diffusible. While this peculiarity enables them to adhere to other colloidal material as well as to precipitates, it does not materially facilitate their isolation, because the attempt of separating them most generally diminishes their power of producing their characteristic reaction, and hence, destroys practically the only means of detecting their presence and identity.

Since ferments are formed from living matter, they have been considered as belonging to the class of the proteins. But, inasmuch as their separation from these substances cannot be effected with certainty, the fact that many of them give the characteristic reactions of proteins cannot serve as a means of identifying them, because these positive results may be due to the protein material which is still adherent to them. Consequently, it must suffice at this time to designate them as organic substances which are derived from proteins and possess a colloidal nature.

Classification of Ferments.—Ferments are almost universally present in nature. So great is their number, that the present discussion must be restricted to those which take a more direct part in the economy of the animal body. Moreover, since we know more about digestion than we do about the processes of cellular assimilation, any enumeration of this kind must be characterized by a preponderance of the digestive enzymes. This fact is largely responsible for the custom of arranging them in accordance with the character of the reaction produced by them, as follows:

¹ Since these topics are exhaustively dealt with in Mathews' and Hammarsten's Textbooks of Physiological Chemistry, I shall discuss these purely chemical data as briefly as possible. More complete references will also be found in Oppenheimer's Handb. der Biochemie, 1910, and "Die Fermente und ihre Wirkungen," 1903; Vernon's "Intracellular Enzymes," 1908; Euler's "General Chem. of the Enzymes" (transl. by Pope) 1912, and Bayliss, "The Nature of Enzyme Action," 1908.

(a) Proteolytic or protein-splitting enzymes, such as pepsin, give rise to a hydrolytic cleavage of the protein molecule.

(b) Lipolytic or fat-splitting enzymes, such as steapsin, cause a hydrolytic cleavage of the fat molecule.

(c) Amylolytic or starch-splitting enzymes, such as ptyalin, produce a hydrolytic cleavage of the starch molecule.

(d) Inverting enzymes, such as maltase, split the disaccharides into monosaccharides and the latter into simpler molecules.

(e) Oxidizing enzymes, such as the oxidases of the tissues, which aid in internal respiration.

(f) Coagulating enzymes, such as rennin, which change soluble into insoluble proteins.

(g) Diaminizing enzymes, such as alanin, which split off an NH_2 group from an amino-acid as ammonia.

In the following table are included some of the ferments with which we are chiefly concerned at the present time, it being the custom to designate them by the name of the substance upon which they act and to affix the letters, ase. This suggestion (Duclaux) has been followed in most instances, the only exceptions being those enzymes which have been recognized for a long time, such as ptyalin, pepsin and trypsin.

	Ferment	Place of action	Character of action
Amylolytic and inverting	Ptyalin	Saliva	Starch—maltose
	Amylopsin	Pancreatic juice	Starch—maltose
	Glycogenase	Liver and muscles	Glycogen—dextrose
	Invertase	Small intestine	Cane-sugar—dextrose
	Maltase	Saliva and small intestine	Maltose—dextrose
	Lactase	Small intestine	Lactose—dextrose and galactose
	Lactic acid ferment	Intestine	Glucose—lactic acid
Lipolytic	Steapsin	Pancreatic juice	Neutral fats—fatty acids and glycerin
	Lipase	Liver, etc.	Neutral fats—fatty acids and glycerin
Proteolytic	Pepsin	Gastric juice	Proteins—peptones and amino- acids
	Trypsin	Pancreatic juice	Proteins—peptones and amino- acids
	Erepsin	Small intestine	Proteoses—amino-acids
	Nuclease	Pancreas, spleen, thymus, etc.	Nucleic acid—purin bases
	Enterokinase	Small intestine	Trypsinogen—trypsin
Deaminizing	Guanase	Thymus, adrenals and pancreas	Guanin—xanthin
	Adenase	Spleen, pancreas and liver	Adenin—hypoxanthin
	Deaminase	Tissues	
	Arginase	Liver and spleen	Amino-acids—oxyacids arginin—urea
	Oxidase	Lungs, liver and tissues	Oxidizes organic substances
	Catalase	Tissues	Decomposes hydrogen peroxide
	Reductase	Tissues	Causes deoxidation

Although still incomplete, this enumeration proves very clearly that almost every reaction necessitates the presence of a particular enzyme. There can be only one reason for this, namely, that they are *specific in their action* and cannot be employed interchangeably to produce one and the same result. Thus, ptyalin changes starch into maltose, but does not affect the fats and proteins, nor even the other carbohydrates. Quite similarly, given a number of closely allied

substances, such as the disaccharides, it will be found that they require several enzymes to convert them into the monosaccharides. Maltose has its own specific enzyme maltase, and lactose a similarly specific enzyme lactase. We also note that a single secretion, such as the pancreatic juice, may harbor a number of ferments, which act separately upon different foodstuffs. To be sure, this specificity is also displayed by other catalyzers, but not quite so definitely as by the enzymes. Thus, it is a well-known fact that the oxidation of hydriodic acid by bromic acid may be effected by means of potassium bichromate but not by iodic acid. Quite similarly, the oxidation of potassium iodid by potassium persulphate may be quickened by copper salts, but not the oxidation of sulphur dioxid by potassium persulphate.

In many cases, these ferments exist within the cell in an inactive form and do not unfold their characteristic properties until they have been discharged into the secretory medium. This antecedent body is known as the proferment or zymogen, and is usually stored in the form of granules. Its activation may be accomplished by inorganic or organic means. In the former instance the intermediary substance is known as an *activator* and the latter as a *kinase*.¹

The Manner of Action of the Ferments.—Catalysis is a common phenomenon in nature and many chemical means and substances may be employed to bring it about. Thus, the disaccharides may be made to undergo hydrolysis into the monosaccharides by simply heating them under pressure to 110°C., and cane-sugar may be inverted into dextrose and levulose by the addition of a weak acid. Either means serves to accelerate the reaction, which otherwise would not take place at all or only with extreme slowness. It is for this reason that catalyzers have been compared to the oil by means of which machinery may be made to run smoothly, *i.e.*, while they do not initiate a certain process, they are in a position to vary its velocity. Consequently, the essential difference between ordinary catalyzing agents and ferments lies in the fact that the latter effect catalysis much more rapidly at moderate temperatures and impart to it a more specific character. In analogy with ordinary catalyzing agents the ferments may cause:

(a) *Hydrolysis*.—This change involves a taking up of water and a conversion of the substance into simpler molecules. As an example of this process might be mentioned the decomposition of the disaccharides, such as maltose, into monosaccharides, one molecule of water being taken up and two molecules of the latter substance being produced. The conversion of fats into fatty acids and glycerin requires three molecules of water. The reverse process is *dehydration*. As an example of this kind might be mentioned the building up of the amino-acids into polypeptides and the complex proteins of the cells.

(b) *Deamination*.—Many tissues possess the power of splitting off an NH_2 group from amino-acid as ammonia and replacing it by H or OH. The reverse process is continuously going on in plants which synthesize proteins from ammonia and a carbohydrate. Some evidence is also at hand to show that this reversion may be effected by animals.

(c) *Decarboxylation*.—This process involves the loss of a molecule of carbon di-

¹Samuely, Handb. der Biochemie, 1908.

oxide from amino-acids and their conversion into the corresponding amine. This change is commonly produced by bacterial action, but may also take place normally as a step in the oxidation of the carbon atoms in the carbohydrates and long chain fatty acids.

(d) *Oxidation and Reduction*.—This process consists in the successive conversion of substances into CO_2 and water under an evolution of energy which is much greater than that derived from the changes enumerated previously.

One of the important deductions to be derived from this tabulation is that catalyzers and especially ferments, not only accelerate decompositions, but are also instrumental in reforming the original substance from its simple end-products. This phenomenon which is known as *reversibility*, was first shown to take place by Croft Hill¹ in two experiments with sucrose and invertase. An especially good example of such a reversible action has been furnished by Kastle and Loevenhart.² By employing the simple ester ethyl-butyrate, they were able to prove that lipase not only hydrolyzes this substance into ethyl-alcohol and butyric acid, but also synthesizes these products of hydrolysis into ethyl-butyrate and water. It appears, therefore, that one and the same enzyme may serve not only to split a foodstuff into its simple constituents, but also to reconstruct the latter into a more complex substance while they traverse the lining of the intestine or enter the tissues. Some investigators assert that this reversibility is something more than a mere establishment of an equilibrium and conforms closely to a true synthesis (Bertrand).

It is also to be noted that ferments act best at an *optimum temperature* of 40° to 50°C . While this is true of all catalyzers, ferments seem to have a more restricted sphere, low and high temperatures being detrimental to them. At 60° to 80°C ., they lose their power, and are destroyed absolutely at 100°C . It is also apparent that the action of catalyzing agents increases with their *surface*. An analogous process is presented by the condensation of a gas upon a solid surface or by the combination of hydrogen and oxygen by means of finely subdivided platinum. In addition, it has been assumed that the unusual power of ferments is due to their ability of forming certain *intermediate products* which, although they do not energize the reaction itself, serve as a means of attaining the end-stage of the catalysis more rapidly. As a last factor influencing ferment action might be mentioned the *number of ferment-molecules* involved. Thus, it has been found that the degree of the change effected in a given period of time, is proportional to the amount of the ferment engaged in this process, and is in a measure independent of the concentration of the substratum. It should be remembered, however, that ferments act in infinitesimally small quantities, and that an abundant supply of them is rather deleterious to the reaction. The reason for this diminution in the effectiveness of a ferment, when present in large amounts, is not

¹ Brit. Med. Jour., 1903, also Mathews and Glenn, Jour. Biol. Chem., ix, 1911, 29.

² Am. Jour. of Physiol., vi, 1902, 331.

easily understood, unless it is assumed that the enzyme then destroys itself in part by autolysis. But this retardation does not take place under all circumstances, because certain fermentations which have come to a standstill owing to the large amounts of ferment present, may again be brought under way by diluting the mixture or by removing the products formed in the course of the reaction.

This "self-inhibition" is closely allied to the inhibition of ferment action by outside means.¹ Thus, it is a well-known fact that these processes may be greatly retarded and abolished by strong acids, alkalies, alcohol, iodine, potassium cyanide, formaldehyde, and the salts of the heavy metals. In many instances, the cells of the different tissues produce a substance which is called *anti-enzyme*. For example, if an enzyme is injected into the blood-stream, certain cells are stimulated to produce an anti-enzyme of a specific kind, so that the serum of this blood may be mixed with the original enzyme with the result that the latter is then quite unable to unfold its characteristic action.

As to the manner in which enzymes increase the velocity of the reaction to which they are specifically assigned, few positive statements can be made. In the first place, it may be assumed that the ferment is combined with the substrate in a loose manner—fitted to it as a key in its corresponding lock.² This simile, no doubt, calls to our minds the interaction between the antigen and the immune bodies, as explained by the side chain theory of Ehrlich. In the second place, it is evident that the ferment is finally removed from the sphere of its action and enters the end-products. This brings the catalysis to an end. These reactions, however, are different from those taking place between various inorganic substances, because the latter are chiefly interactions between electrolytes. Thus, the molecules of sodium chlorid are broken up into their cations Na which are charged positively and move toward the cathode or negative pole, and their anions Cl which are negative and move toward the anode or positive pole. Since the organic foodstuffs, namely, the proteins, carbohydrates and fats, are not electrolytes, their reactions cannot be regarded as analogous to these almost instantaneous ionic movements. They take place more slowly and are in reality molecular interactions. When only one substance is being transformed, it constitutes a *unimolecular reaction*. As an example of this kind might be mentioned the conversion of starch into sugar. The velocity of the reaction is measured in this case in terms of substance transformed, *i.e.*, in gram-molecules per liter in the unit-time of one minute. But, as the amount of substance acted upon is gradually diminished, the velocity of the reaction must also be reduced in a proportionate measure. In those cases in which two substances are changed simultaneously, as occurs in the decomposition of esters under the influence of an alkali, a *bimolecular reaction*

¹ Porter, Quart. Jour. of Exp. Physiol., iii, 1910, 375.

² Emil Fischer, Zeitschr. für physiol. Chemie, 1898.

takes place. The velocity of the reaction is then proportional to the square of the amount of the substance.

The Function of Saliva.—Saliva possesses a two-fold action, namely, a physical one and a chemical one. It moistens the mucous surfaces of the mouth as well as the food, thereby facilitating its mastication and deglutition. In addition, it acts as a solvent allowing sapid substances to excite sensations of taste, and as a cleaning agent of the oral cavity. The former is of special importance, because it serves to evoke those stimuli which give rise to the psychic secretion of gastric juice and a certain satisfaction in eating. These are its only functions in those animals, such as the horse, sheep, ox and dog, in which a true digestive ferment is not present.¹ The substance more particularly concerned in this purely mechanical process is mucin. In man and some of the herbivora, however, it also possesses a moderate chemical action by virtue of its enzyme ptyalin. This ferment acts exclusively upon starch, converting it into maltose through several intermediary stages, such as soluble starch or erythro-dextrin which gives a red color with iodine, and achroo-dextrin which gives no color with iodine. But since ptyalin does not attack cellulose, it is imperative that the starch be well cooked beforehand so as to destroy its capsular investments. Moreover, while the warmth of the mouth causes the starch to be reduced very rapidly, a considerable portion of even the boiled starch invariably escapes salivary digestion, because mastication is usually practised in a hasty and careless manner. The solid starch which is ingested in farinaceous foods, bread, and biscuits, is only slightly affected by the saliva and practically no hydrolysis is instituted by this secretion.

Ptyalin is most effective at 37°C. and in a neutral or weak acid medium, but a slightly alkaline medium is not unfavorable to its activity. Inasmuch as its action is destroyed by such small amounts of acid as 0.003 per cent. HCl, it might be supposed that it must lose its effectiveness as soon as it enters the stomach. This is not the case, because the freshly swallowed food forms a coherent mass which is not easily penetrated by the gastric juice, and besides, some time must elapse before a sufficient quantity of the latter has been secreted to fill the relatively inactive cardiac end of the stomach. During the interim, the ptyalin continues its reductions and it is safe to say that from 30 to 40 minutes must elapse before its action is stopped completely. Meanwhile, the largest part of the available starch has been hydrolyzed and, while a certain proportion of unreduced starch may escape salivary digestion, it is later on subjected to the action of the amylopsin of the pancreatic juice. Unboiled starch, on the other hand, escapes even this powerful diastatic ferment and enters the feces unutilized.

The Function of Gastric Juice.—The action of the gastric juice is due partly to its acid and partly to the combined action of its acid and ferments. It may be said that:

¹ Küss, Ref. Maly, 1898, Zebrowski, Pflüger's Archiv, cx, 1905, 105, and Palmer, Am. Jour. of Physiol., xli, 1916, 483.

(a) *It is Antiseptic.*—Whenever carbohydrates are ingested, a certain number of micro-organisms are also taken in. These give rise to fermentations, in the course of which considerable quantities of lactic acid may be produced. The subsequent outpouring of hydrochloric acid destroys many of these organisms, as well as others of pathogenic character, but some of them always escape into the intestine (*bac. acidi lactici*); where they find a more suitable medium for their growth.

(b) *It Inverts Sucrose into Glucose and Fructose.*—This action is not due to the presence of an invertase in this juice, but to the hydrochloric acid and such inverting enzymes as may be present in the food ingested.¹

(c) It contains a *fat-splitting enzyme or lipase*. Its action in this regard is two-fold, because the hydrochloric-pepsin combination dissolves the protein constituents and investments of the fat-cells, and allows the fat to escape and to coalesce. In addition, a small quantity of lipase is present which splits the emulsified fat into glycerol and fatty acids, but naturally, the hydrolysis going on in this organ is insignificant when compared with that effected in the intestine by the pancreatic juice. The origin of this lipase is somewhat in doubt; some claim that it is regurgitated with the contents of the small intestine and some, that it is an actual product of the gastric mucosa. It is of much greater importance to the suckling than to the adult.

(d) *It Curdles Milk.*—This property of gastric juice is due to its ferment rennin or chymosin² which, as has been mentioned above, appears to be formed separately from the pepsin.³ It initiates a two-fold process, namely, the conversion of caseinogen into casein, and the combination of the altered casein with the soluble calcium salts to form a curd.⁴ This action is greatly accelerated by the hydrochloric acid which in itself is capable of precipitating caseinogen, but this acid is by no means an indispensable factor as is provided by the fact that the curdling of milk also takes place in a neutral or alkaline medium, but not after the milk has been boiled. Moreover, the curd produced by rennin in the presence of calcium salts, exhibits certain properties which are quite different from those exhibited by the acid precipitate. At all events, the newly formed casein is subjected later on to the action of pepsin in the same way as other proteins. It seems, however, that the curdling of milk takes place before much acid has been secreted; in fact, milk is not an effective stimulant for the secretion of hydrochloric acid, and is used, therefore, to allay hyperchlorhydria. To the suckling, the curd is of profound importance, because it tends to retain this important nutritive material for a longer time in the stomach so that it may undergo thorough digestion.⁵

(e) It contains a *proteolytic enzyme*. This is its most important property. The combination of pepsin and hydrochloric acid converts the proteins of the food into peptones, but does not change their constituent polypeptides into their ultimate cleavage products, the amino-acids. This change is effected by hydrolysis, the first stage being the formation of acid meta-protein, and the next step, the formation of proteoses, such as albumoses, globuloses, vitelloses, etc., as follows:

Protein

Acid meta-protein

Propeptone or proteose	{ Primary { Proteo-proteose { Hetero-proteose Secondary, Deutero-proteose
Peptone or polypeptides	

¹ Widdicombe, Jour. of Physiol., xxviii, 1902, 175.

² Hammersten, Maly's Jahresb., 1872.

³ Porter, Jour. of Physiol., xlii, 1911, 389.

⁴ Van Slyke, New York Med. Jour., 1909, Proc., Soc. Exp. Biol. and Med., 1911.

⁵ Gmelin, Pflüger's Archiv, ciii, 1904, 618.

Proteoses and peptones are classified in accordance with their physical characteristics, such as their solubility and salting out. In the following table a native protein albumin is contrasted in this respect with its peptic end-products:

Action of						
	Heat	Alcohol	Nitric acid	Ammonium sulphate	Copper sulphate	Diffusibility
Albumin	Coagulation	Precipitation and coagulation.	Precipitation in the cold; not easily dissolved on heating	Precipitation after complete saturation	Violet color	None
Proteoses	No coagulation	Precipitation, but no coagulation	Precipitation in the cold; easily dissolved on heating	Precipitation after saturation	Rose red color	Slight
Peptones	No coagulation	Precipitation but no coagulation	No precipitation	No precipitation	Rose red color	Readily

Upon the constituents of connective tissue and other allied protein substances, the pepsin-hydrochloric acid combination acts as follows:

(a) Collagen, a constituent of bone and white fibrous and areolar tissue, is converted into gelatin, gelatoses and gelatin-peptones. Since these tissues contain much fat, this foodstuff is separated from its investments.

(b) Elastin, a constituent of elastic tissue, is not acted upon under ordinary conditions.

(c) Mucin, a constituent of the ground-substance of connective tissue, is converted into peptone-like substances.

(d) Nucleo-proteins are changed into a protein portion and a nuclein portion. The former is then converted into proteoses and peptones, whereas the latter is precipitated in an insoluble form. On phospho-proteins it acts in a somewhat similar manner.

The Function of Pancreatic Juice.—This secretion plays an even more important part in digestion than the gastric juice, because it contains several powerful enzymes. Its function may be summarized as follows:

(a) *Proteolytic.*—This property is imparted to it by its enzyme trypsin which differs materially from pepsin, because it gives rise to a more rapid as well as more thorough catalysis. To begin with, it is to be noted that trypsin acts in an alkaline medium, whereas pepsin acts in an acid medium. Moreover, while the former produces the same initial conversions of the protein molecule as the latter, it does not stop here but reduces the peptones still further into their constituent amino-acids, such as leucine, tyrosine, alanine, aspartic acid, glutamic acid, arginine, tryptophane, and others. It is also to be observed that this conversion is effected so rapidly that the formation of the primary proteoses can scarcely be detected, while the secondary derivatives come into prominence almost immediately. In place of acid-metaprotein, however, we now obtain alkaline-metaprotein. In addition, a reduction of elastin takes place which is not effected at all by the gastric

juice. When the peptone stage has been passed, the biuret reaction is no longer obtained. Regarding the degree of alkalinity existing in the duodenum much uncertainty prevails. While pancreatic juice is a strongly alkaline secretion, owing to its content in sodium carbonate, it must be remembered that the alkalinity of this medium must be changed repeatedly by the entrance of the fresh acid chyme. Its reaction may then become neutral, but the action of trypsin cannot be unfavorably affected by a condition of this kind, because most effective artificial media are usually made by dissolving commercial trypsin in only 0.2 to 0.3 per cent. of sodium carbonate. It is true, however, that larger amounts of this enzyme require a larger amount of this salt. It has been pointed out above that the conversion of trypsinogen into trypsin necessitates the presence of enterokinase or calcium salts.¹ It is also said that erepsin may be present at times in pancreatic juice, because when inactivated, this secretion may digest casein but not other proteins.

(b) *Amylolytic*.—Pancreatic juice contains an amylase, known as amylopsin, which hydrolyses the starches more rapidly than ptyalin. Even unboiled starch is affected by it under formation of erythro-dextrin and maltose. In a nearly neutral medium this disaccharide is converted further into the monosaccharide dextrose or glucose. This additional hydrolysis is dependent upon the presence of a second ferment, maltase.

(c) *Lipolytic*.²—The powerful fat-splitting enzyme of pancreatic juice is called steapsin. It changes neutral fats, such as the triglycerides of palmitic, stearic and oleic acids, into the corresponding fatty acids. Since this medium possesses an alkaline reaction, these fatty acids unite with the alkaline bases to form soaps which then appear as films upon the outer surfaces of the fat-globules and prevent them from coalescing. These emulsions assume a more stable character in the presence of proteins, and colloids.

(d) *Milk-curdling*.³—Pancreatic juice also possesses the power of clotting milk, but this action may not be due to the presence of a special enzyme. It differs in its character from that of rennin.

The Function of Bile.—The velocity with which lipolysis takes place in the small intestine, is considerably increased by the presence of bile, the active agent concerned in this process being the bile salts. These act in two ways, namely by their solvent action on fatty acids and soaps and secondly, by their property of diminishing the surface tension between the fat and the water. This enables the intestinal juices to enter into closer relation with the globules of fat. Consequently, the digestive value of bile lies in its adjuvant power of furnishing a more appropriate medium for the interaction between the steapsin and the fatty acids than the pancreatic juice alone could possibly constitute. In some animals, it also contains a weak amylolytic enzyme.

Bile also serves as a vehicle for the fats during their absorption. This statement implies that the end-products of lipolysis traverse the intestinal epithelium not merely in an emulsified form, but as fatty acids or soaps and glycerin. This gives rise to a "circulation of the bile," because some of the biliary substances are again absorbed and made use of later on in the manner just indicated.

While the bile salts possess mild antiseptic qualities, the bile itself

¹ Schepowalnikow, Dissertation, St. Petersburg, 1899, and Bayliss and Starling, Jour. of Physiol., xxviii, 1902, 375.

² Connstein, Ergebn. der Physiol., iii, 1904.

³ Kühne Verh., med. Verein, Heidelberg, iii, 1881.

has no definite influence of this kind. In other words, the fact that it diminishes putrefaction in the intestine, is due chiefly to its power of hastening the absorption of those substances which are most likely to give rise to these processes. Bile is to a certain extent excretory. In addition, it aids in neutralizing the acid chyme and in precipitating its unpeptonized protein. This renders the chyme more viscid and retards its progress through the intestine, thereby augmenting absorption.

The Function of the Intestinal Juice.—The principal action of the intestinal secretion is exerted upon the carbohydrates. Its invertase changes cane-sugar into glucose and levulose or fructose, whereas its maltase¹ transforms maltose into glucose.² A special enzyme, called lactase,³ is abundantly present in young animals for the purpose of converting milk-sugar into galactose and glucose. The ferment enterokinase (Pawlow) which activates trypsinogen, is widely distributed through the intestine. A similar body is erepsin⁴ which increases the hydrolysis of the first products of the proteolysis and rapidly changes albumoses and peptones into amino- and diamino-acids. Moreover, since a great deal of fat may be split up in the small intestine even in the absence of both bile and pancreatic juice, it is assumed that it contains a lipase of relatively feeble power. The sodium carbonate, in which it is rather rich, must, of course, aid in the formation of soaps from the fatty acids.

This fact brings up the important point that the secretions in the intestine form a suitable medium for the growth of bacteria, contrary to the gastric juice which by virtue of its acidity attenuates micro-organisms. Some of them, however, reach the intestine in spite of the gastric juice and produce here certain enzymes, the actions of which are very similar to those of the ferments normally contained in the local secretions. In some instances, these putrefactive organisms also give rise to more specific reactions, as follows:

(a) *On Carbohydrates.*—The most important reaction is the lactic acid fermentation which is chiefly responsible for the formation of intestinal gases. It usually takes place in two stages which may be represented by the following two equations:

Vegetable food increases this fermentation, the cellulose being split into carbonic acid and urethane.

(b) *On Fats.*—Some bacteria possess a lipolytic action and are capable of producing lower acids, such as valeric and butyric. It cannot surprise us, therefore,

¹ Rosenbloom, Conn. Biolog. Chem., xiv, 1913, 241, and Hammarsten, *Ergebn. der Physiol.*, 1905.

² Röhrmann, *Pflüger's Archiv*, xli, 1887, 424.

³ Halliburton, *Textb. of Chem. Path. and Physiol.*, 1891.

⁴ Cohnhein, *Zeitschr. für phys. Chemie*, xxxvi, 1902, 13, and Vernon, *Jour. of Physiol.*, xxxii, 1904, 32.

to find that the contents of the lower small intestine may become acid, in fact, this acidity may on occasions invade higher segments without, however, materially impairing pancreatic digestion. The latter, as we have seen, does not require an especially high alkalinity.

(c) *On Proteins*.—Some bacteria are capable of splitting proteins into amino-acids, liberating during this process such substances as indol (C_8H_7N), scatol (C_9H_9N), and phenol (C_6H_6O). These animo-acids are further reduced by them into their corresponding amine bases by the process of decarboxylation which consists in removing carbon dioxid from their carboxyl ($COOH$) group. In this way, leucine may be converted into its base iso-amylamine, as follows:

This base, and especially the oxyphenylethylamine derived from tyramine, possesses a pressor action similar to that of adrenalin. The former substance is a constituent of ergot. It is also of interest to note that the enzymes of fungi, such as those affecting grasses and fruits, are capable of decarboxylizing some of these bases. In spite of the formation of the aforesaid acids, however, the contents of the large intestine become alkaline. This change is due to the fact that some of the bacteria generate ammonia which again neutralizes the organic acids.

CHAPTER LXXXIV

THE MECHANICS OF DIGESTION

A. MASTICATION AND DEGLUTITION

General Consideration.—In those animals in which digestion is chiefly intracellular, the chemical processes necessitate a mechanical manipulation of the food which purposes to effect its reduction into smaller masses and its steady onward movement, so that it may be successively subjected to the different secretions. Leaving out of consideration the celenterata, in which the digestive and vascular systems are still incompletely separated, as well as the echinodermata, in which this separation is complete, it may be said that the arthropoda are the first to present an alimentary canal which shows definite variations in its caliber, corresponding to the stomach, and small and large intestines of the higher animals. Glandular organs are placed along this canal which seem to be homologous with the salivary glands and the liver-pancreas of the higher forms. Possibly the simplest alimentary system among the vertebrates is presented by the fishes. It consists of a stomach, the glands of which furnish an acid proteolytic secretion, and a fully differentiated intestine with a series of digestive fluids possessing different actions.

The alimentary canal of birds exhibits several peculiarities, such as

the crop and the double stomach. The former appears as an enlargement of the proximal segment of the esophagus, and serves as a reservoir for the food, performing a function similar to that of the oral pockets of the squirrels and allied animals. Besides, this pro-stomach furnishes a secretion which institutes a swelling of the kernels and a destruction of their cellulose investments. Of special interest is the fact that this organ also secretes a milk-like fluid which serves as food for the young during the first two or three weeks of their life. It contains a considerable amount of fat which is derived from the desquamated and degenerated epithelial lining. The stomach of these animals consists of two segments, namely, a glandular pro-ventriculus, and a muscular ventriculus. The former furnishes an acid secretion rich in pepsin, whereas the latter reduces the food into smaller fragments. In this function it is aided very materially by the solid substances, such as granules of sand, which these animals are in the habit of ingesting with their food.

The alimentary canal of the mammals presents as its two principal characteristics the division of the stomach into two or four cavities, and the varying length and caliber of the small and large intestines. The carnivora are characterized by a preponderance of the small intestine, and the herbivora by a preponderance of the large intestine. Some of the mammals, such as the rodents and cetaceæ, are in possession of a stomach consisting of two pouches, while that of the ruminating animals consists of four compartments. In the latter, the esophagus terminates in a vestibular enlargement which communicates with the first and second gastric cavities. The food enters chiefly the first cavity, where it is intermingled with older material and is in part forced into the second compartment. After 30 to 70 minutes (cow), small amounts of the now somewhat softened material are projected into the mouth to be remasticated. Most of this material is finally converted into a liquid mass which upon being reswallowed is directed into a muscular furrow through which it attains the third and fourth cavities. Its still unreduced portion is retained in the first compartment to be remasticated if necessary at the rate of 6 to 8 times in the course of 24 hours, each act of mastication lasting from 45 to 60 minutes. Liquids, on the other hand, may enter all four compartments simultaneously. The capacity of the cow's stomach varies between 160 and 230 liters, four-fifths of which are apportioned to the first two chambers.

The alimentary canal contains secretory as well as muscular elements which are held together by varying amounts of connective tissue. Its length varies considerably in different animals, being shortest in the carnivora and longest in the herbivora. In general, the ratio between its length and that of the entire body is, in man, as 1 : 5 or 1 : 6; in the dog, as 1 : 6; in the cat, as 1 : 4; in the cow, as 1 : 20, and in the sheep, as 1 : 27. The mucous membrane lining the digestive tract presents a surprisingly large surface to the simplified foodstuffs.

Thus, it has been ascertained that the mucosa of the dog, if spread out in a single layer, covers more than one-half of the body-surface.

In man, the muscular stratum of the alimentary canal is made up of smooth muscle tissue which is arranged in two layers, an outer longitudinal and an inner circular. This arrangement is departed from in the mouth, pharynx and stomach, where oblique fibers are added; moreover, the mouth, pharynx, upper part of the esophagus, and end of the rectum, contain numerous strands of striated muscle. Internally, the circular layer of smooth muscle tissue lies in relation with areolar tissue, containing blood-vessels, lymphatics and nerves. It forms the submucous coat. This in turn is clad with epithelium, constituting the continuous mucous lining of the entire digestive tract. Externally, the longitudinal layer of smooth muscle tissue is enveloped by a thin serous layer, the peritoneum. The mechanical processes associated with digestion, are mastication, deglutition, and the churning movements of the stomach, small intestine and large intestine.

Mastication.—The articulation between the mandible and maxillary bone is classified as a double condyloid joint. Owing to the looseness and strength of its capsular ligament, the articular surfaces of these bones may be moved freely upon one another, allowing the mandible to execute three types of movements which may be classified as (a) depression and elevation, (b) projection and retraction, and (c) deviation from side to side. Its raising is effected by the combined contraction of the temporal, masseter, and internal pterygoid muscles, and its depression by gravity and the action of the digastric muscle in conjunction with the mylohyoid and geniohyoid. At this time, the hyoid bone is fixed by the contraction of the omohyoid and sternohyoid muscles. When both external pterygoids contract simultaneously, the jaw is protruded. The opposite movement is effected by the internal pterygoids. The contraction of only one set of these antagonistic muscles gives rise to a deviation of the jaw toward one side or the other.

The grinding motions of mastication consist chiefly in a lowering and raising and a lateral deviation of the jaw, the food being kept between the molar teeth by the action of the tongue, the orbicularis oris and the buccinators. The action of these parts is controlled by a reflex center which is situated in the medulla oblongata and includes the nuclei of the motor nerves innervating the aforesaid muscles, namely, those of the trigeminal, facial and hypoglossal nerves. On the afferent side, this center is connected with different receptors, and particularly with the spindles of the muscles concerned in this act. By this means, the force and character of the movements of the jaw are reflexly regulated. The closure of the lips and depression of the tongue and jaw during inspiration may give rise to a negative pressure in the oral cavity, approximating 25 to 50 cm. H_2O .

The importance of mastication differs in different animals. In the carnivora, the food is rapidly projected through the mouth and is

swallowed in rather large masses, whereas in the herbivora, and especially in the ruminating mammals, it is slowly reduced into the smallest possible fragments. The omnivora, such as man, occupy an intermediate position in this regard. These differences are associated with definite peculiarities in the shape and structure of the parts concerned in mastication. Thus, we find that the teeth of the carnivora are well adapted to catch the food, while those of the ruminants present all the characteristics of grinders. In man, the incisors are to hold and to divide the food, whereas the canines divide it, and the bicusps and molars macerate it. The development of these parts proceeds in the same manner as that of the hairs. A continuous thickening of the epithelium takes place along the gums which grows into the corium of the mucosa and forms the *dental germ* or *dental lamina*. Further thickenings and growths give rise to the *special dental germ* from which the milk teeth are developed. Each germ contains a vascular papilla and is eventually separated from the general mucous membrane by a vascular septum, which is known as the *dental sac*. The papilla is finally transformed into the dentine and pulp of the growing tooth, while its enamel is deposited upon this core by the epithelial cells of the dental germ. Later on, as the tooth grows outward, its root is formed which is then covered with cement.

In man, the teeth appear in two sets, a temporary one and a permanent one. The first consists of the so-called milk teeth. They are twenty in number and appear between the 5th and 30th month. Their time of appearance, however, varies considerably, being subject to family characteristics, and the condition of the child. The first to appear are the two central incisors below (5th to 9th month), next the four upper central teeth (8th to 12th month); then the other two lower central teeth and the four front double teeth (12th to 18th month). The four incisors follow next (18th to 24th month), the upper being known as the "eye teeth" and the lower as the "stomach teeth." The four back double teeth which complete the first set, break through between the 24th and 30th month. Every one of the milk teeth is replaced in the course of time by a permanent tooth. This change begins at about the 7th year and proceeds in about the same sequence as the formation of the temporary set. In addition, each maxilla acquires six new teeth, three on each side. These are the permanent molars. The last of these, or wisdom teeth, appear about the 20th year, but have been known to be delayed until the 30th year and later. The permanent set, therefore, consists of thirty-two teeth.

Deglutition.—In brief, the process of mastication consists in a mechanical reduction and anointment of the food which eventually leads to the formation of the *bolus*. This rounded pulpy mass of food is then projected into the stomach by the process of deglutition or swallowing. In general, it may be said that the onward movement of the food through the alimentary canal is effected by peristaltic motion, but the gross character of this muscular activity differs somewhat in the different segments of this channel. The act of deglutition is divided into three stages. The first is oral in its character and terminates with the passage of the bolus through the pillars of the fauces. The second concerns the constituents of the pharynx and ends with

the entrance of the food into the upper extremity of the esophagus. The third is restricted to the esophagus and terminates with the arrival of the food in the cardiac end of the stomach. It is also to be noted that the first is effected by striated muscle, and constitutes, therefore, a voluntary act, whereas the last two are due almost wholly to the contraction of smooth muscle tissue and are, therefore, involuntary or reflex in their nature. In spite of these functional differences, however, deglutition is a continuous act and no pauses occur between its successive phases. Further, the initiation of the first invariably means the completion of the third, although some persons may acquire a limited volitional control over the second.

Immediately before the beginning of the first stage, the process of mastication is suspended. Respiration is arrested after a slight contraction of the diaphragm, constituting the so-called "respiration of swallowing." The lips are closed and the maxillæ closely approximated. The tip of the tongue is then elevated and pressed against the inner aspect of the upper gum. The muscles effecting this movement are the inner longitudinal strands of the tongue which are controlled by the hypoglossal nerve. This elevation then progressively involves the entire tongue from before backward, forcing the bolus in the same direction through the fauces. This movement brings into play the *musc. mylohyoideus* (*nerv. trigeminus*) which raises the hyoid bone, as well as the *musc. styloglossus*, *musc. palatoglossus* and, in an indirect manner, also the *musc. stylohyoid* (*nerv. facialis*). The latter elevate the back of the tongue, so that its inherent muscle strands may progressively obstruct the posterior extent of the oral cavity.

As soon as the bolus has been forced through the fauces, it is brought under the control of the three sphincters of the pharynx which direct it into the upper extremity of the esophagus. This process necessitates a temporary obstruction of the nasal and laryngeal cavities. The closure of the first is brought about by the simultaneous contraction of the *levator palati* and *palato-pharyngeus* muscles, the uvula being at this time forced in contact with the posterior pillars, and the latter in turn with the upper posterior wall of the pharynx. The closure of the epiglottidean orifice necessitates the elevation of the hyoid bone and an upward and forward movement of the larynx. The former is brought about by the contraction of the *geniohyoid*, anterior belly of the *digastric* and *mylohyoid*, and the latter, by the contraction of the *thyrohyoid*. At this time, the back of the tongue is pulled backward by the contraction of the *styloglossus*, thereby forcing the epiglottis downward across the laryngeal orifice. A still firmer closure of this passage is effected by the contraction of the *reflector epiglottis* and *aryepiglotticus*, as well as by the constriction of the glottis itself. Stuart and McCormick,¹ however, have shown that the removal of the epiglottis does not seriously interfere with the act of

¹ Jour. of Anat. and Physiol., 1892; also: Kanthak and Anderson, Jour. of Physiol., xiv, 1893, 154.

swallowing, because the backward movement of the tongue and upward deviation of the larynx usually suffice to prevent an ingress of food into the respiratory passage.

At about the level of the closed epiglottidean orifice, the bolus is brought under the influence of the middle and inferior constrictors of the pharynx, the successive contractions of which force it into the upper segment of the esophagus. It has been shown by Kronecker and Falk¹ that fluids pass more rapidly and usually do not require a concerted action of the parts just enumerated; in fact, the movements of the back of the tongue generally suffice to direct them through the relaxed upper segment of the esophagus into its lower portion. It is for this reason that some persons, under abolition of the pharyngeal reflexes, are able to pour considerable quantities of water almost directly into the cardia. This also explains the fact that the erosions produced by the hasty intake of corrosive fluids, are usually most severe in the lower esophagus.

It has been shown by Cannon and Moser² that the progression of semi-solid food through the esophagus takes place much more leisurely, and is effected by peristaltic waves which proceed from above downward. It will be remembered that the smooth musculature of this membranous tube is arranged in two layers, namely, as an inner circular and an outer longitudinal coat. A peristaltic wave, however, does not consist solely of a contraction of the circular fibers, but presents itself in all instances as a progressive wave of constriction which is anteceded by a wave of relaxation, the bolus being driven ahead of the contracting band of muscle tissue in the direction of least resistance. But since the upper and even the middle segments of the esophagus contain a few strands of striated muscle tissue, it cannot surprise us to find that the progress of the bolus is more rapid above than in the vicinity of the cardia. According to Schreiber,³ the entire act of peristalsis for semi-solid food consumes about 6 seconds, about one-half of this period being occupied by the passage of the bolus through the lower segment of the esophagus.

A very appreciable retardation also results at the cardiac sphincter which guards the gastric orifice of the esophagus. This circular ring of smooth muscle tissue relaxes only under the gradually increasing force of the newly arrived bolus. Obviously, this mechanism prevents the sudden ingress of the food into the stomach as well as its immediate projection into the fundic portion of this organ.⁴ On listening over the region of the cardia when fluid is taken, two sounds are heard, the first of which is produced by its sudden projection

¹ Archiv für Anat. und Physiol., 1880, 296.

² Am. Jour. of Physiol., i, 1899, 435, and Eykman, Pflüger's Archiv, xcix, 1903, 513.

³ Archiv für exp. Path. und Pharm., xlv, 1901, 414.

⁴ Beaumont's observations upon Alexis St. Martin, also Hertz, Guy's Hosp. Rep., London, 1907.

through the esophagus, and the second, by its gurgling through the cardiac orifice.

Nervous Control of Deglutition.—The act of swallowing involves the voluntary mechanisms of the mouth and pharynx, and the involuntary mechanism of the esophagus. Consequently, deglutition may be treated as a reflex act which is evoked by the projection of the bolus against the mucosa of the fauces and pharynx, regions which are innervated, on the one hand, by the trigeminus and, on the other, by the glossopharyngeus. Besides these normal "pace-makers," this passage also includes several other areas which upon mechanical stimulation give rise to deglutition.¹ The afferent channels involved in this reflex lie in the second division of the trigeminus, the glossopharyngeus and the pharyngeal branches of the superior laryngeus, whereas the center occupies a place in the upper part of the medulla oblongata. The motor fibers are contained in the hypoglossal, facial, trigeminus, and vagus nerves.

This enumeration shows very clearly that the parts involved in deglutition, are arranged segmentally, but the sensory and motor nerves controlling them, are coördinated in so precise a manner that no interruption can possibly result in the orderly progression of the wave of contraction. Thus, Meltzer² has shown that the peristaltic wave does not require an integrity of the muscular tube so long as the nervous mechanisms have not been interfered with, while Mosso³ has proved that a ligature applied to the esophagus, does not block this wave, provided the reflex circuits have not been broken. An even more striking proof of the successive involvement of the different segments of this membranous tube has been furnished by Mikulicz. It concerns a man whose esophagus had been resected in part for the removal of a carcinomatous growth. The lower segment of this tube was made to open through a wound in the neck, the purpose of this arrangement being to allow the food to reach the stomach in the normal way. It was found, however, that its introduction through this opening did not incite peristalsis, whereas it was moved onward immediately if the act of swallowing was instigated in the normal way by the corresponding movements of the mouth parts.

An interval of at least 1.0 second must intervene between the successive acts of swallowing, otherwise certain inhibitor influences will arise which effectively block the succeeding peristalsis. This inhibition is said to be under the control of the glossopharyngeus, because it is a well-known fact that the normal pace-maker of deglutition is represented by the nucleus of this nerve. Evidently, this refraction allows each act of deglutition to be completed before the beginning of the next, although it may happen at times that new food reaches the cardiac sphincter before the material swallowed previ-

¹ Kahn, *Archiv für Physiologie*, 1903; Suppl., 386.

² *Brit. Med. Jour.*, 1906.

³ Moleschott's *Untersuchungen*, 1876.

ously, has had sufficient time to escape into the stomach. This interference invariably gives rise to painful sensations and regurgitation of the food.

It should also be noted that the afferent impulses which determine the activity of the center of deglutition, cause a stoppage of the respiratory movements. This is important, because an inspiratory motion occurring during deglutition, might draw the food into the respiratory passage, whereas an expiration occurring at this time, might force it into the nasal cavity. The fact that this inhibition of respiration is effected with the help of the glossopharyngeal nerve, may be proved by stimulating the fauces and neighboring regions of the pharynx, either mechanically or electrically. We have previously seen that an analogous reaction may be produced by the excitation of the mucous membrane lining the nasal (trigeminus) and laryngeal cavities (sup. laryngeal nerve). Thus, it cannot surprise us to find that the introduction of a stomach-tube gives rise to an almost immediate inhibition of respiration which persists even after a severe cyanosis has been established. Repeated attempts at swallowing, however, will temporarily remove the inhibition and allow the subject to replenish the oxygen content of his blood. A close reflex relationship also exists between the center of deglutition and the cardiac center, as is evinced by the fact that the act of swallowing increases the rate of the heart.

FIG. 511.—DIAGRAMMATIC REPRESENTATION OF THE STOMACH.

C, Cardiac end; F, fundus; P, pylorus; D, duodenum; CS, cardiac sphincter; SA, sphincter antri pylori; PS, pyloric sphincter; V, valvulae conniventes.

B. THE MOVEMENTS OF THE STOMACH

The Movements of the Fundus and Pylorus.—The muscular coat of the stomach consists essentially of an outer longitudinal and an inner circular layer. To these are added in certain areas of this organ an inner layer of obliquely placed muscle strands which serve to strengthen its wall along its anterior and posterior surfaces below the cardia. The *layer of circular strands* is the heaviest of all and is of greatest functional importance. At the pyloric and esophageal poles of the stomach it suddenly increases in thickness, forming here the so-called pyloric and cardiac sphincters. A third band of circular fibers invests the stomach at the junction between its fundic and pyloric portions, *i.e.*, about 7 to 10 cm. above the pylorus. It is known as the sphincter

antri pylori and corresponds to the point of origin of the peristaltic movements of the pyloric end of this organ. It is also of interest to note that this muscular band is more highly constricted in some persons than in others, giving rise to the so-called hour-glass stomach. While this condition may be inherited, it is more commonly caused by excitations of the gastric mucosa, such as may arise in consequence of erosions and ulcers. The *outer longitudinal* layer continues at the cardia with the longitudinal fibers of the esophagus, and is heaviest along the greater and lesser curvatures of the stomach. At the pylorus it passes over into the longitudinal layer of muscle tissue of the duodenum.

Anatomically, therefore, the stomach may be divided into two compartments, namely, into its pyloric portion or antrum pylori, comprising about one-fifth of the entire organ, and its much larger fundic portion and cardiac recess. This division also possesses a correct physiological basis, because the antrum pylori is infinitely more active than the fundus, so much so, in fact, that the latter is commonly regarded as the reservoir of the former. A more thorough study of these movements may be made with the help of the following methods:

(a) Observation of the manner in which the gastric contents are discharged through a duodenal fistula.¹

(b) Introduction of a small rubber bag into the cavity of the stomach which is connected with a recording tambour.²

(c) Inspection of the interior of the stomach through a fistulous opening (Beaumont).

(d) Observation of the stomach through a wound in the abdominal wall, a piece of mica being inserted in the opening to protect the stomach against external stimuli.

(e) Observation of the excised stomach under proper conditions of moisture and temperature.³

(f) Observation of the stomach by means of the Röntgen-rays after the ingestion of food containing subnitrate of bismuth.⁴

The empty stomach is small in size, but its walls cannot collapse, because a thin layer of frothy material remains interposed between them. This froth consists of mucus and a few cubic centimeters of gastric juice. At this time, the intragastric pressure is zero. The entrance of food then separates its walls more widely but chiefly those of the cardia, because the newly swallowed material collects at first directly below the esophageal orifice. Here it may remain in a relatively undisturbed condition for nearly an hour, salivary digestion going on unhindered during the interim. This fact is well illustrated by the experiments of Grützner,⁵ who fed rats successively with semi-

¹ Hirsch, *Zentralbl. klin. Med.*, 1892.

² Ducceschi, *Arch. ital. de Biol.*, xxvii, 1897, 61.

³ Hofmeister and Stutz, *Archiv für Exp. Path. und Pharm.*, xx, 1885, 1.

⁴ Roux and Balthazard, *Compt. rend.*, 1897, and Cannon, *Am. Jour. of Physiol.*, i, 1898, 359, and xii, 1904, 387.

⁵ Pflüger's *Archiv*, cvi, 1905, 463.

solid food of different color and found it later on arranged in concentric strata in the vicinity of the esophageal orifice. The material ingested first was pushed downward and outward toward the gastric wall, while that eaten last, occupied the central extent of this space. This slow whirling about of the food serves to bring its different portions into more intimate contact with the walls of the fundus and, therefore, also with the gastric juice. Eventually, when even its innermost mass has been completely acidified, the action of the ptyalin ceases, while that of the pepsin begins. As far as the mechanical function of the fundus is concerned, it may therefore be said that this gastric segment acts merely as a reservoir for the digestive tract. Considerable amounts of food may be stored in it which are then fed, hopper-like, to the pyloric mill for mechanical and chemical reduction. This function does not require an unusual muscular activity, because gravity and the pressure exerted by the food as it slowly oozes through the relaxed cardiac sphincter, no doubt suffice to force it toward the sphincter antri pylori. Later on in the course of gastric digestion, its walls contract more forcibly in order to empty its more dependent portions, a regurgitation of the food being prevented at this time by the closure of the cardiac sphincter. But the pressure present in this compartment at the height of digestion, rarely exceeds 6 to 8 cm. of water.¹

The mechanical conditions existing in the pyloric end of the stomach, differ widely from those just described. Food having been received, a band-like constriction appears at the sphincter antri pylori which gradually increases in depth until the fundus has been completely shut off from the pylorus. This circular constriction then moves slowly toward the pyloric sphincter, where it arrives about 20 seconds later. Some time before it disappears another one develops and progresses in the same direction. In this way, a number of peristaltic waves are produced which force the food toward the pylorus, whence it recoils along the wall toward its starting point. As many as three of these waves may be observed at one time. Thus, one may just be disappearing at the pylorus, while another is still at some distance from it, and a third is just forming at the antrum. Although the intensity and frequency of these waves vary with the time of gastric digestion, they usually recur at intervals of about 10 seconds (cat) and invariably proceed from the fundus toward the pylorus. Anti-peristaltic movements occur only under pathological conditions.

FIG. 512.—SECTION OF FROZEN STOMACH OF RAT DURING DIGESTION TO SHOW THE STRATIFICATION OF FOOD GIVEN AT DIFFERENT TIMES. (Grützner.)

¹ Kelling, *Zeitschr. für Biol.*, xlv, 1903, 161; and Schlippe, *Deutsch. Arch. klin. Med.*, lxxvii, 1903, 450.

In man these movements may be studied with the help of the Röntgen-rays, the person to be examined having previously ingested a mixture of koumiss and subnitrate of bismuth. Most commonly, these

FIG. 513.—ROENTGEN CINEMATOGAMS OF THE HUMAN STOMACH. (*Kästle, Rieder, and Rosenthal.*)

examinations are made in the standing position, so as to be able to note the lower boundary of the stomach, and to be able to determine

whether this organ possesses a muscular power sufficient to force its contents through the pyloric orifice. Obviously, the latter is situated at this time somewhat above the level of the general cavity of the pylorus. Moreover, when standing erect, the stomach assumes more nearly the shape of a suspended stocking and allows the gases to escape very freely, whereas, when lying down, the esophageal orifice assumes a position somewhat below the level of the general gastric cavity and entraps any gases that may have been formed.

The Evacuation of the Gastric Contents.—The purpose of the peristaltic movements of the stomach is to mix the food with the gastric juice, and to reduce it eventually into a liquid which is known as the chyme. In this form, the gastric contents are then ejected through the relaxed pyloric orifice into the duodenum. The muscular activity which is required to accomplish this end is somewhat different from that previously noted in the course of the formation of the chyme. It consists essentially in a contraction of the horizontal and oblique layers of muscle tissue which employ the cardia as a fixed point and raise the fundus above the general level of the pylorus. Meanwhile, the pylorus continues its peristaltic activity, and forces its contents toward the pyloric orifice. Naturally, the chyme cannot escape as long as this sphincter remains closed and must in this event be whirled back along the sides of the gastric wall.

Two reasons may be assigned for the continued closure of this sphincter, namely: (a) the gastric contents still contain solid masses which exert a mechanical influence upon the mucosa of this region, and (b) the gastric contents have not as yet been sufficiently acidified.¹ Contrariwise, if the gastric contents have been thoroughly liquefied and acidified, these mechanical and chemical stimulations cease and allow the sphincter to relax. The chyme is then ejected into the duodenum, being here thrown against the upper surfaces of the valvulae conniventes which extend as transverse flaps partially across the lumen of this passage. The presence of acid in the duodenum then effects the closure of the pyloric orifice. Thus, the ejection of chyme is immediately followed by a constriction of the sphincter until the acid liquid in the duodenum has again been neutralized. The ejection of chyme is then repeated. Consequently, it may be concluded that the opening and closing of the pyloric sphincter is dependent upon the physical condition of the gastric juice as well as upon the relative degrees of acidity in the cavities of the stomach and duodenum. Consequently, the evacuation of the stomach is not a continuous act, but takes place at intervals until its cavity has been completely emptied. The nervous mechanism concerned in this reflex act, lies in the domain of the plexus gastro-duodenalis.

The Time of Evacuation of the Gastric Contents.—The preceding discussion must show immediately that the time of evacuation of the gastric contents is subject to considerable variations which depend

¹ Hirsch, *Zentralbl. für innere Med.*, 1901.

not only upon the force and frequency of the peristalsis, but also upon the character of the food ingested. Thus, Cannon¹ has shown that the carbohydrates begin to leave the stomach soon after their ingestion and require only about one-half the time necessary for the complete digestion of the proteins. Fats, when ingested alone, remain in the stomach for a long time. Quite similarly, the simultaneous intake of different foodstuffs markedly interferes with the evacuation of those which otherwise escape very rapidly. Accordingly, if protein is fed before the carbohydrates, the latter are retarded, whereas fat tends to hinder the progress of both. In general, however, it may be said that a moderate meal, consisting of all foodstuffs, should be out of the stomach after four hours, and its ejection should begin within an hour after its ingestion. The first portion of this chyme, therefore, may have arrived at the ileocecal valve before its last portion has trav-

FIG. 514.—SHADOWS OF THE HUMAN STOMACH OBTAINED WITH THE AID OF THE RÖNTGEN RAYS 15 MINUTES, 1 HOUR, AND 4 HOURS AFTER INGESTION OF THE BISMUTH MEAL.

ersed the pyloric orifice. These facts imply that a stomach which still contains material at the end of five hours, either lacks tonicity or is unable to discharge on account of some obstruction, possibly a pyloric stricture. Water and isotonic salt solutions are passed into the duodenum very rapidly. Hypertonic solutions and other drinks, such as coffee and tea, require a somewhat longer time.² As far as the intake of moderately large quantities of water during meals is concerned it may be stated in general that it serves the purpose of hastening the formation of chyme, although it may also tend to dilute the gastric juice to such an extent that its digestive power is unduly diminished. In view of the results of Carlson, however, showing that very abundant amounts of hydrochloric acid and pepsin are held in reserve, the latter possibility is rather remote, and should be taken into consideration only when a hypochlorhydria is present.

Gastro-enterostomy.—The operation of gastro-enterostomy consists in uniting the lower duodenum directly with the stomach distally to its sphincter antri pylori. Physiologically, it is of importance to

¹ Am. Jour. of Physiol., xii, 1904, 387.

² Arch. für Exp. Path. und Pharm., lii, 1905, 370, and Müller, Zeitschr. für diät. und phys. Ther., viii, 1905.

remember that unless the fistulous communication is very large, the food will nevertheless pass through the pylorus. Consequently, the pyloric obstruction must be rather complete before the fistula can serve its purpose. Secondly, it has been observed in animals that some of the material which has left the stomach by way of the pylorus again enters this organ through the fistulous communication. Thirdly, the outpouring of the acid gastric juice into intestinal segments which are normally not directly exposed to it, may lead to erosions and ulcerations of the mucosa, and especially if the blood- or nerve-supply have in any way been interfered with during the operation. Consequently, such a communication should not be established in the absence of organic disease of the pylorus.

Vomiting.—The act of vomiting is a complex reflex in which different muscles take part and which is usually preceded by a sensation of nausea, a reflex secretion of saliva, and other symptoms of a more general character. In the suckling it consists essentially of a contraction of the musculature of the stomach and a relaxation of the esophagus and presents, therefore, the simplest possible details. In the adult, on the other hand, other factors are brought into play, chief among which is the abdominal press. The latter consists in a spasmodic contraction of the abdominal muscles, inclusive of the diaphragm, following a short inspiration and closure of the glottis. It is apparent, however, that in the adult the stomach plays a rather subordinate part, as is evinced by the fact that the retching movements occurring at the beginning of the act of vomiting, which are wholly of gastric origin, are altogether too weak to eject the gastric contents. Moreover, it has been shown by Gianuzzi that this act cannot be evoked in curarized animals, because this agent paralyzes the muscles of the abdomen. In addition, it has been proved by Magendie that vomiting also results in animals whose stomach has been replaced by a bladder filled with water.

During the act of vomiting the peristalsis is abolished, although intense movements of this kind may take place shortly beforehand. Irregular retching motions then result which, however, do not seem to be antiperistaltic in their character. The essential factor concerned in vomiting, is the production of a high intragastric pressure, which, as we have just seen, is the direct result of the contraction of the abdominal muscles and smooth musculature of the stomach. The pylorus is tightly closed at this time, while the cardiac sphincter and esophagus are relaxed.¹ An eructation of gas frequently precedes this act, in fact, many animals such as the dog hasten its occurrence by distending the stomach with freshly swallowed air. Vomiting also necessitates a forward movement of the hyoid bone and larynx, as well as a projection of the mandible. Both measures serve to straighten the channel of ejection. Although the nasal cavity is partly protected against the ingress of vomited material by the con-

¹ Openchowski, *Archiv für Physiol.*, 1889, 552.

traction of the upper constrictor and the approximation of the pharyngeal wall and pillars of the fauces, the force of the ejection is sometimes so great that this hindrance is overcome.

The act of vomiting is controlled by a special center situated in the medulla oblongata. On the efferent side, it is connected with the different muscles mentioned previously and, on the afferent side, with various local and general receptors. Thus, it is a well-known fact that the sight and smell of offensive food or objects may serve as adequate exciting causes, and that it may also be evoked by the mechanical stimulation of the fauces and pharynx, as well as by irritations of the gastric and intestinal mucosa. Even extragastric stimuli in the form of abdominal tumors and the gradually enlarging uterus of pregnancy may instigate it. Apomorphin produces its characteristic effect by a direct stimulation of the vomiting center.

The Innervation of the Gastric Musculature.—The stomach is wholly under the control of the autonomic nervous system, the distal-most fibers of which are expanded between its circular and longitudinal layers of muscle tissue into the plexuses of Meissner and Auerbach. This organ, therefore, is well equipped with a local reflex mechanism which is destined to regulate its various motor activities. Thus, it has been ascertained that the excised stomach, if kept under proper conditions of moisture and temperature, may be made to contract upon local stimulation, and may even show a spontaneous activity. Under normal conditions, this peripheral sympathetic mechanism is connected with the central nervous system by way of the two vagi and splanchnic nerves. The former terminate in the vicinity of the cardia in two ramifications which are known as the ventral and dorsal gastric plexuses. From here fibers pass over to the left suprarenal plexus of the splanchnic system, as well as to the neighboring region of the lesser curvature. At the present time, however, no evidence is at hand to show that these plexuses also send fibers directly to the greater curvature or to the region of the pylorus. The latter seem to derive their innervation from the celiac ganglion of the solar plexus by way of the celiac and splenic plexuses.

It can no longer be doubted that the vagi nerves embrace musculo-motor nerves for this organ. This is proved by the fact that their stimulation above the diaphragm evokes well marked contractions which involve chiefly its pyloric segment and possess all the characteristics of regular peristaltic waves. While it is commonly stated that the splanchnic nerves exert an inhibitory influence upon the movements of this organ, it cannot be said that this view possesses a satisfactory experimental basis. Inasmuch as these nerves contain powerful vasoconstrictors, the relaxing effect sometimes observed upon their stimulation, may in reality be caused by a diminution in the gastric blood-supply.¹ Since the musculo-motor function of the vagi nerves has been well established, it may be said that their nuclei,

¹ Burton-Opitz, Pflüger's Archiv, xxxv, 1910, 205.

in conjunction with some additional ganglion cells, form a center which regulates the activity of the intragastric reflex mechanism. This medullary center is connected with different afferent channels through which sensory impulses are enabled to reach it. They are here converted into motor impulses and relayed to the intragastric plexuses. Thus, Wertheimer¹ has shown that the stimulation of the central end of the sciatic nerve gives rise to a reflex inhibition of the gastric movements. Acceleratory and inhibitory effects may also be produced by psychic influences, such as delight, anxiety, anger and fright.

C. THE MOVEMENTS OF THE INTESTINES

The Movements of the Small Intestine.—Since the entrance of air into the abdominal cavity, the evaporation of the serous fluid and the lowering of the temperature generally induce a refractory state in this organ, various precautions must be taken in order to avoid this motor disturbance. Thus, it has been advocated to insert an oval piece of glass or mica in the incision in the abdominal wall, or to open the peritoneal cavity in a bath of warmed saline solution. In rabbits it is possible to thin the abdominal wall in such a degree that the abdominal organs may be inspected without actually opening this cavity. These methods have been supplemented at an early date by graphic procedures, consisting in fastening a soft rubber bulb to the surface of the abdomen or in inserting it directly into the intestinal canal. Air transmission being employed in both these cases, the recording tambour accurately registers the displacements of the air from the bulb. Another means which is now extensively used, is the fluoroscope which allows us to follow the food in its course through the alimentary canal by virtue of the fact that subnitrate of bismuth when mixed with the ingesta, does not allow the Röntgen rays to pass. Lastly, it is possible to study excised segments of intestine under proper conditions of moisture and temperature. They may then be connected with recording levers and pneumographs. A special piece of apparatus of this kind is the enterograph.

The arrangement of the musculature of the small intestine is simple; an outer, relatively thin coat of horizontal muscle fibers lies in relation with an inner circular coat. It should be noted, however, that the structure of its different segments is not absolutely uniform, but shows certain variations with regard to the thickness of the muscle tissue. Thus, it will be found that the jejunum is large in caliber and very muscular, while the ileum is narrow and possesses much thinner walls. Similar differences are encountered in the different segments of the duodenum.

The movements occurring in the intestine, consist of peristaltic and pendular motions. Obviously, the contraction of the circular

¹ Arch. de physiol., norm. et path., 1892, also, Doyon, *ibid.*, 1895.

fibers must constrict its lumen, whereas the contraction of the longitudinal fibers must render that particular segment more bulky and enlarge its capacity. Ordinarily, however, these two movements are combined into what is known as the *peristaltic wave*, which consists of a zone of constriction and an antecedent zone of relaxation. These peristaltic waves may proceed either from above downward or from below upward. The former constitute the *regular peristaltic waves* and the latter, the *antiperistaltic waves*. We shall see later that antiperistalsis is the chief movement of the beginning portion of the large intestine, while regular peristalsis is the principal movement of the small intestine. Antiperistalsis is observed here only under abnormal conditions. A second type of movement executed usually by the small intestine, is the so-called *pendular motion*. It consists of alternate constrictions and relaxations of neighboring segments of the gut, which are repeated with a definite regularity or rhythm.

FIG. 515.—DIAGRAM TO SHOW THE EFFECT OF THE RHYTHMICAL CONSTRICTING MOVEMENTS OF THE SMALL INTESTINE UPON THE CONTAINED FOOD.

A string of food (1) is divided suddenly into a series of segments (2); each of the latter is again divided and the process is repeated a number of times (3 and 4). Eventually a peristaltic wave sweeps these segments forward a certain distance and gathers them again into a long string, as in (1). The process of segmentation is then repeated as described above. (Cannon.)

When the chyme is ejected into the duodenum, it is forced against the upper surfaces of the valvulae conniventes which stretch across the lumen of the subpyloric canal in the form of incomplete transverse partitions. In consequence of this initial impediment to its rapid onward flow, the chyme is collected in a single mass well above the orifices of the biliary and pancreatic ducts. Now begins its subdivision into smaller portions by the pendular or rhythmic movements. A comprehensive study of these has been made by Grützner¹ who was able to analyze them by mixing insoluble substances, such as nitrate of bismuth, with the ingesta. More recently, Cannon² has studied them with the help of the Röntgen rays. Constrictions appear here and there which split the formerly large mass into numerous smaller ones. Moreover, these constrictions appear in a perfectly regular order so that the original mass is divided first into two, then into four, then into eight, and more. These smaller portions are then reunited into

¹ Pflüger's Archiv, lxxi, 1898.

² Am. Jour. of Physiol., i, 1898, and vi, 1902.

larger ones. This rhythmic play continues for some time at the rate of 20 to 30 in a minute (cat) until the chyme has been thoroughly mixed with the intestinal secretions,¹ and naturally, the cessation of these alternate constrictions and relaxations must leave the now rather liquid material again reunited into a single mass. A regular peristaltic wave then sweeps it onward into a lower segment of the small intestine, where the pendular movements are repeated with the same result. While this mechanical and chemical reduction of the food is continued far into the ileum, the material already reduced is absorbed; in fact, absorption begins very soon after the entrance of the chyme into the duodenum and reaches its height in the jejunum and upper ileum. In the lower ileum, on the other hand, most of the assimilable material has already been removed, but naturally, much depends upon the character of the ingesta, and the tonicity of the intestinal musculature.

It should also be noted that the peristalsis and pendular motion undoubtedly facilitate absorption in a mechanical way, because they tend to increase the flow of the lymph and blood. Secondly, they tend to bring the individual villi into a more intimate relation with the intestinal contents. As far as the regular peristaltic wave is concerned, it should be mentioned that it occurs in two forms, namely, as a slowly advancing contraction (2 to 3 cm. per sec.) which again disappears at a distance of about 5 cm. from its place of origin, and as a more rapid contraction which may cover a distance of 10 to 15 cm. and more. The former, therefore, remains more localized and serves to disseminate the material so that it may be acted upon later on by the pendular motions. The latter, on the other hand, serves to remove the completely digested material into more distant segments situated nearer the ileocecal valve. No definite statements can be made regarding the degree of pressure which may be developed by these waves, but since the fecal material is in a liquid state, it may be surmised that the energy required to move it is very slight. This deduction is upheld by the experiments of Cash² which show that a weight of 5 to 8 gm. applied to the surface of the intestines, suffices to block the progress of the feces.

Antiperistaltic movements occur in the small intestine only under abnormal conditions, such as may arise in consequence of obstructions by foreign bodies and tumors, or as a result of an invagination or kinking of the entire gut. If the lesion is a high one, the fecal material is often forced into the stomach, whence it is expelled by the process of vomiting.

The Nervous Control of the Intestinal Movements.—While these peristaltic movements may be evoked almost anywhere along the intestine, they begin as a rule high up in the duodenum, and hence, it would not be incorrect to speak of a "pace-maker" of peristalsis. In all these instances, the stimulations are local in their character and may

¹ Magnus, Pflüger's Archiv, cxi, 1906, 152.

² Proc. R. Soc., London, 1887.

be brought to bear either upon the muscle tissue or upon the nervous tissue. The early experiments of Bayliss and Starling¹ have led strength to the first view, which is embodied in the so-called *myogenic theory* of the origin of peristalsis, because it could be shown that the application of nicotine does not destroy these movements. The experiments of Cohnheim² and Magnus,³ on the other hand, favor the *neurogenic theory*, which holds that the nervous tissue is the recipient element. Thus, it was found that isolated segments exhibited these movements even after the removal of their mucosa and submucosa, and that the separation of the inner and outer coats of muscle tissue destroyed them only in that layer which was disconnected from the plexus of Auerbach. In addition, Yanase⁴ has shown that the intestines of the embryo rabbit and human fetus do not begin to move until the aforesaid nervous elements have made their appearance.

While this controversy seems to favor the neurogenic theory, it may be best to confine ourselves for the present to the statement that the peristaltic movements result in consequence of the stimulation of the intestine by the fecal material and that they may arise in any one of its different segments. The result is a diphasic wave, consisting of a zone of constriction which is anteceded by a zone of relaxation. Consequently, the peristaltic movement represents a true reflex response which is made possible by the coördinated action of the local nervous mechanism. The latter may in turn be influenced by afferent impulses arising in other parts of the body, because it is a matter of common experience that emotions or sensory impressions of different kinds may inhibit or accelerate the activity of the intestinal musculature. These impulses, in all probability, descend through the vagus system and terminate in the mesenteric ganglion of the solar plexus, whence they are relayed to the intra-intestinal mechanism by way of the mesenteric plexus. Regarding the latter, it has been proved by Burton-Opitz⁵ that it contains efferent as well as afferent fibers for the intestine. The fact that the vagus nerve constitutes the preganglionic path of these musculomotor impulses seems definitely proved, because its stimulation evokes strong contractions of the intestine. The claim that the splanchnic nerve is the musculo-inhibitor nerve of the intestine, need not be discussed at length, because it lacks a satisfactory experimental basis. As has been stated above, the flaccidity of parts ensuing in consequence of the stimulation of this nerve, may be due to its vasoconstrictor action and the anemia resulting therefrom. To summarize: (a) the intestine is in possession of a local nervous mechanism which renders it relatively independent of the central nervous system, (b) systemic reflexes are made possible by the communications

¹ Jour. of Physiol., xxvi, 1901, 125.

² Zeitschr. für Biol., xxxii, 1899.

³ Ergebn. der Physiol., 1908.

⁴ Pfüger's Archiv, cxix, 1907, 451.

⁵ Ibid., cxxxv, 1910, 245.

existing between this sympathetic ramification and central parts by way of the mesenteric ganglion of the solar plexus and the vagi nerves, and (c) the successive segments of the intestine are enabled to act in unison, because the plexus of Meissner and Auerbach is arranged in the form of successive reflex circuits which are correlated with one another.

The last contention is based upon the experimental evidence that peristaltic waves may be incited almost anywhere along the intestine which then progress in a downward direction through its successive segments. Additional light has been thrown upon this question by Mall who has resected and reversed certain segments of the small intestine so that their formerly lower ends became their upper. At autopsy, these animals invariably exhibited a fusiform distention of the intestine above the line of the upper suture and an accumulation of fecal material which in many cases had resulted in necrosis, perforation, and peritonitis. It is evident, therefore, that this inversion of an intestinal loop causes the regular peristalsis to cease at the upper line of sutures. Moreover, if an oval ball of wood is inserted into the upper end of one of these inverted segments, it is again expelled through the same opening, whereas its insertion through the lower orifice gives rise to a peristaltic wave which moves it in the direction of the stomach. The question of whether the intestinal movements of man can at all be compared with those of other animals, may be answered in the positive; in fact, Carvallo, as well as Küpferli¹ state that they are identical.

FIG. 516.—DIAGRAM TO SHOW THE POSITION OF THE ILEOCECAL VALVE.

J, Ileum; C, cecum; A, orifice of the proc. vermiformis; AC, ascending colon; H, haustrum.

The Movements of the Large Intestine.

—The function of the large intestine is so widely different from that of the small intestine that these two parts may almost be considered as separate organs. In the carnivora the process of digestion and absorption is practically completed at the ileocecal valve, while in the herbivora these processes continue in all their intensity distally to this point. The omnivora occupy an intermediate position, but since the human large intestine is relatively long and possesses a capacious cecal vestibule and peculiarly indented colon, it more nearly resembles that of the herbivorous animals. The *ileocecal* valve is a sphincter formed of a heavy band of muscle tissue and two membranous flaps which are unequal in size and do not close firmly. The fact that the contents of the cecum may be forced back into the ileum with great ease, shows that it does not form a very efficient sphincter. At the same time, it must be admitted that it

¹ Zeitschr. für Röntgenkunde, xiv, 1912.

impedes the progress of the contents of the ileum sufficiently, so that the latter can advance into the cecum only in larger masses and under a slight increase in pressure effected by the periodic peristaltic movements of the ileum.

The large intestine may be divided into four parts, namely, the cecum with its vermiform appendix, and the ascending (proximal), transverse (intermediate), and descending (distal) portions of the colon. The movements observed here are very similar to those previously noted in the upper gut, *i.e.*, they consist of peristaltic and pendular motions. It is to be emphasized, however, that the latter are now of little importance, whereas the antiperistaltic movements are even more prominent than the peristaltic.¹ It is also obvious that the large intestine is much more quiescent than the small intestine, a

FIG. 517.—SHADOWS OF THE HUMAN LARGE INTESTINE OBTAINED BY MEANS OF THE RÖNTGEN RAYS.

I, Entrance of the contents of the ileum into the cecum and colon. II, the material has progressed through the transverse colon as far as the splenic flexure, some has escaped into rectum. III, the large intestine outlined by means of a solution of subnitrate of bismuth injected through the rectum.

fact which is in perfect agreement with the time required by the food to traverse this channel. To illustrate, while the human stomach and small intestine which measure about 7 m. in length, retain the food for only about 7 to 9 hours, the large intestine which is only 1.5 m. in length, cannot be passed in a much briefer time than 20 hours. Consequently, the passage of the food from the mouth to the anus occupies in all from 25 to 30 hours. An active alimentary canal, therefore, would evacuate its contents once in about every 24 hours.

On entering the ascending colon, the chyme incites antiperistaltic waves which force it into the cecum. A regular peristaltic wave then moves it upward toward the hepatic flexure, whence it is again thrown back into the cecum by the antiperistalsis. These back and forth movements continue for some time until the contents have lost most of their water and gradually escape in a semisolid state into the transverse colon. It is to be noted especially that these antiperistaltic motions do not oppose the regular waves, but alternate with them and

¹ Jacobi, *Archiv für exp. Path. und Pharm.*, xxvii, 1890.

give rise to a harmonious back and forth motion of the feces. Furthermore, since the proximal colon is subdivided into successive recesses by incomplete transverse partitions, a whirlpool effect is produced which carries the contents from haustrum to haustrum. It is for this reason that the movements in the proximal colon and cecum are often designated as *haustral churning*.

Gradually as the water is absorbed, the fecal material assumes a more solid consistency and escapes into the transverse colon, whereas its more fluid portion is forced back into the cecum. Eventually, however, all of it is lodged in the transverse colon and is held here until forced into the rectum by long and forceful peristaltic waves. This segment, therefore, plays the part of a storehouse and hence, it cannot surprise us to find that any retardation of the feces must result in a loss of an excessive quantity of water and a firm lodgment of these masses in the haustræ. Its gradually increasing weight then gives rise to a sagging which causes the hepatic flexure to assume a much lower level than the splenic flexure. This condition is not at all uncommon and is responsible for the peculiar outline of this part of the intestine when observed with the Röntgen rays. It then displays the contours of a snake when assuming the position of striking. The descending colon and rectum are usually empty and are filled only a short time before the beginning of the act of defecation.¹ This filling of the rectum is accomplished by two or three powerful long peristaltic waves which begin in the transverse colon and slowly traverse the descending colon, forcing the feces into the rectal receptacle. They are usually accompanied by noises which have been designated by Kussmaul as the "*tormina intestinorum*." In accordance with Scharz,² it may be concluded that these waves are the direct cause of defecation, because they force a certain amount of fecal material into the rectum which then serves as the initial stimulus to the receptors initiating this process.

Cannon³ divides the large intestine into two parts, the first of which includes the very active cecum and ascending colon and the second, the relatively inactive transverse and descending colons. This line of demarcation transects it distally to the hepatic flexure. Furthermore, Elliott and Barclay-Smith⁴ have shown that the intense antiperistaltic movements of the upper large intestine are present in a great variety of animals, and are especially prominent in the herbivora in which the cecum plays the part of a large thin-walled reservoir for the food while undergoing bacterial decomposition.

Defecation.—The distal portion of the colon leads into the sigmoid flexure and rectum. Under normal conditions, the latter receives

¹ Roith, Anat. Hefte, 1902, and Reider, Fortschr. auf dem Geb. der Röntgenstrahlen, 1912.

² Münchener med. Wochenschr., 1911.

³ Am. Jour. of Physiol., xxix, 1911, 238.

⁴ Jour. of Physiol., xxxi, 1904, 272.

fecal material very shortly after arising, because the food which has found lodgment in the transverse colon during the preceding night, is then aided by gravity and a renewed irritability of the receptors in exciting those long peristaltic waves which finally move it into the vicinity of the anal orifice. The gradually increasing mass of rectal contents finally stimulates the mucosa in a mechanical manner and evokes those muscular responses which are required for its expulsion. If the feeling of fulness experienced at this time, is neglected, the walls of the rectum relax more fully, so that a much greater excitation will be required to make them contract again. In man, Hertz¹ has shown

FIG. 518.—SCHEMA TO SHOW THE INNERVATION OF THE RECTUM AND INTERNAL SPHINCTER OF THE ANUS, AND THE FORMATION OF THE HYPOGASTRIC PLEXUS. (After Frankl-Hochwart and Fröhlich.)

that the intrarectal pressure may rise to 30 and 40 mm. Hg. before the act of defecation is actually initiated.

While defecation is a reflex phenomenon, it also embraces a definite voluntary factor. The former consists in peristaltic contractions of the rectum and the inhibition of the internal sphincter, whereas the latter comprises the relaxation of the external sphincter and the activation of the abdominal press. Under normal conditions, these reflexes may be counteracted if necessary, by volition, but only until the sensory stimuli become so powerful that they are able to overcome the volitional efforts. The reflex center for defecation is situated in the lumbar segment of the spinal cord, whence efferent and afferent

¹ Guy's Hosp. Rep., 1907.

nerve fibers pass to the musculature of the rectum and the internal and external sphincters. By means of these channels, this center is brought into functional relation with different local receptors which may either augment or inhibit its activity. In the latter case, the sphincters are relaxed. It is connected with the cerebrum by means of different afferent and efferent paths, so that volition, emotions, and various sensory impulses, may be brought to bear upon it.

The powerful band of smooth muscle tissue forming the internal sphincter, receives its motor supply from the hypogastric plexus by way of the *nervus erigens*, and its inhibitory supply from the same source by way of hypogastric nerve. These nerves also embrace sensory fibers from the same region, as well as sensory and motor fibers for the rectum. When severed, the excitation of the central end of the *nervus erigens* gives rise to an inhibitory effect which is made possible with the help of the hypogastric nerve. Quite similarly, the stimulation of the central end of the divided hypogastric nerve produces motor results through the intervention of the *nervus erigens*.¹ The external sphincter is composed of striated muscle tissue and is innervated by the *nervi hemorrhoidales inferiores* which are derived from the *nervus pudendus* and sacral spinal nerves. This muscle acts in unison with the levator ani and other perineal muscles, and aids in restoring the everted mucous membrane of the anus after the completion of defecation.

¹ Frankl-Hochwart and Fröhlich, Pflüger's Archiv, lxxxi, 1900, 420.

SECTION XXVII

ABSORPTION

CHAPTER LXXXV

THE ABSORPTION OF THE REDUCED FOODSTUFFS FROM THE ALIMENTARY CANAL

General Discussion.—The term absorption refers more particularly to the process by means of which the simplified foodstuffs are transferred from the lumen of the alimentary canal into the absorbing channels, *i.e.*, into the blood-capillaries or the lacteals. It is to be remembered, however, that certain animals also take in materials through their skin, and that absorption from the different body-cavities is a common phenomenon. If we confine ourselves at this time to the foodstuffs, it is to be noted first of all that water, salts, and the simple sugars are dialyzable without digestion, whereas others must be changed so as to be able to pass through the intestinal epithelium. This brings in a definite element of time; digestion and absorption going on side by side, because certain substances begin to pass into the body long before the chemical and mechanical reductions of all the different foodstuffs have actually been completed. Moreover, while some of the digested material may be taken up in the mouth, stomach, and large intestine, by far the largest amount is absorbed in the small intestine.

In endeavoring to obtain an idea regarding the factors concerned in absorption, we find first of all that they are resident in a layer of epithelial cells, which, physiologically considered, really form a part of the external envelope of the body. Through these the simplified foodstuffs must pass in order to gain access to the fluids of the body. Until not so many years ago it was believed that the forces by means of which this transfer is effected, consist of filtration, diffusion, and osmosis. In the course of time, however, it has become evident that many of these phenomena cannot be explained upon this basis and hence, physiologists finally took recourse to a purely vitalistic hypothesis. As emphasized repeatedly on previous occasions, it is for us to accept an intermediate view which not only acknowledges the above physical principles, but also recognizes the occurrence of certain intracellular processes, regarding which our knowledge is as yet ex-

tremely imperfect. The latter consist in microphysical and micro-chemical reactions and not in phenomena which might more rightly find a place in metaphysics. While the work in molecular physics, such as that of DeVries, Van't Hoff and Fischer, has gone far to clear up the nature of these processes, it must be admitted that our explanations are still based upon generalities.

Diffusion, Osmosis, Dialysis.—The term *diffusion* is applied to the spreading about or scattering of molecules through media allowing this movement. Thus, if a solution of a salt is placed in a receptacle and a layer of water is carefully allowed to run over it, it will be found after a time that a certain number of the molecules of the salt have entered the overlying water and have established a medium of uniform composition throughout. This spreading out also takes place if two solutions of different salts are brought into contact with one another. A uniform mixture is the final result. Next we proceed to interpose between the solution and the water an animal membrane, such as a piece of intestine, urinary bladder, swim-bladder, or an artificial membrane made by allowing ferrocyanide of potassium to come in contact with cupric sulphate in an unglazed piece of porcelain. The result of this interaction is a layer of ferrocyanide of copper.¹ Such membranes may be absolutely impermeable, completely permeable, or partially permeable to water and its constituents. The first allows no diffusion at all, whereas the second permits it to occur freely in both directions. This narrows this discussion down to membranes of semi-permeable character, namely, to those which allow a free interchange of water but not of the dissolved substances. Consequently, if the water and the salt solution are separated by a membrane of this kind, the molecules of water will gradually pass through its pores into the solution. This phenomenon is called *osmosis*.

Quite similarly, we may fill a thistle tube with a solution of magnesium sulphate, close its large orifice with an animal membrane, and place it in water so that the level of the latter corresponds precisely with that of the said solution. Water then passes into the thistle tube, causing the level of the magnesium sulphate solution to rise until its height indicates a considerable back pressure against the membrane. This pressure

FIG. 519.—A SIMPLE OSMOMETER.

The receptacle contains water, and the cell a solution of magnesium sulphate. As the molecules of water are drawn through the semi-permeable membrane, the level of the $MgSO_4$ solution rises.

¹ Morse and Frazer, Am. Chem. Jour., xxxiv, 1905, 1, also Hedin, Pflüger's Archiv, lxxviii, 1899, 205, Höber, ibid., lxxi, 1898, 624, and Denis, Am. Jour. of Physiol., xvii, 1906, 35.

which is known as the *osmotic pressure*, is responsible for the passage ("pulling") of the molecules of water through the pores of the membrane. In general, it may be said that the osmotic pressure of a solution is proportional to its molecular concentration, *i.e.*, to the number of molecules of the dissolved substance in a given volume of the solution. This fact implies that it differs with the character of the solutions employed. Its force, however, is considerable at all times. Thus, it has been determined that a 1.0 per cent. solution of cane-sugar at 0°C. exerts a pressure of 493 mm. Hg. Regarding its origin little is known, but it is commonly believed that it is due to the

FIG. 520.—DIALYSER, CONSISTING OF A TUBE OF PARCHMENT PAPER IMMERSED IN A VESSEL THROUGH WHICH A CONSTANT STREAM OF STERILE DISTILLED WATER CAN BE PASSED. (Wroblewski.)

kinetic energy of the moving molecules. The greater their attraction, the greater this pressure.

While such simple arrangements as have just been described, actually exist in our body, the most common interchanges take place between crystalloids and colloids. The process of transferring these substances through an animal membrane interposed between the solution containing them and the water, is known as *dialysis*. In this case, the crystalloids traverse the membrane and enter the water, while the colloids do not. But since the membranes in our body are only approximately semi-permeable, they allow water to go through

with ease and besides, also the substances in solution. The latter, however, pass with much greater difficulty. For this reason, the osmotic flow of water to the side of the crystalloid is associated with a passage of the molecules of the latter into the water on the other side of the membrane. These counter streams eventually lead to an equalization of the concentration of the fluids on the two sides of the membrane, as well as to an equalization of the osmotic pressure and a cessation of the osmosis. Only diffusion then continues in both directions.

The osmotic pressure of a solution may be calculated by ascertaining the amount of the substance present in it and the degree of the dissociation of its electrolytes. A much simpler method is to determine its freezing point, because the freezing point of water is lowered by substances held in solution, and the degree of lowering is proportional to the molecules and ions present in it. A comparison of the osmotic pressures of different solutions may be made by noting their influence upon certain vegetable and animal cells.¹ Thus, if erythrocytes are brought in contact with the solution to be tested, they either swell, or shrink, or remain normal. Inasmuch as these cells are ordinarily contained in blood plasma, this medium must be isotonic to them, *i.e.*, it must possess the same osmotic pressure as the red corpuscles. No osmotic interchanges then take place. It may, therefore, be reasoned that any solution in which they retain their normal size and shape, is *isosmotic* or *isotonic* to them as well as to the blood plasma. A *hyperosmotic* or *hypertonic* solution is one possessing a greater osmotic pressure, and a *hyposmotic* or *hypotonic* solution, one possessing a slighter osmotic pressure than these cells or the blood-serum. In the first instance, these cells will lose water and shrink and in the latter, acquire water and swell up.²

Electrolytes.—The law of osmosis as previously stated, is practically identical with the law of Boyle pertaining to the diffusion of gases. The latter states that the pressure of a gas is proportional to its density, *i.e.*, to the number of the molecules in a given volume of the gas. Like the osmotic pressure, the gaseous pressure remains proportional to the absolute temperature and the sum of the partial pressures of the constituents of the mixture. A slight discrepancy between gas pressure and osmotic pressure, however, is produced by the fact that the molecules of many substances, when in solution, are dissociated into two or more parts which are designated as ions. These ions are charged electrically and may be made to arrange themselves in accordance with their potential by passing an electrical current through the solution. Thus, it will be found that sodium chlorid gives rise to Na ions and Cl ions, the former being positive and the latter negative. If an electrical current is now passed in a definite direction through this solution, these ions migrate until a perfect

¹ McClendon, *Physical Chemistry and Vital Phenomena*, 1917, and Bayliss, *Principles of Gen. Physiology*, 1915.

² Overton, *Nagel's Handb. der Physiologie*, 1907.

electrical series has been established by the alternate position of plus and minus elements. Water, on the other hand, is not easily dissociated and hence, cannot serve as a good conductor of electricity. The same is true of sugar. Upon these differences is based the division of substances into electrolytes and non-electrolytes. Now, since an ion plays the same part in the production of osmotic pressure as a molecule, it will be seen that a solution of an electrolyte must exert a proportionally greater osmotic pressure, because it contains a greater number of particles consisting, on the one hand, of molecules and, on the other, of ions.

The Diffusion of the Proteins.—Conditions in our body are complicated still further by the fact that its different fluids do not contain solely crystalloids, but also other substances, such as proteins. The latter are practically indiffusible through animal membranes, although most of them are soluble in water, weak salt solutions, and dilute acids and alkalies. Moreover, they form compounds with metallic salts, acids or alkalies and, when in solution or pseudo-solution, can be converted into an insoluble form by various simple means, such as changes in the reaction and temperature, shaking, and the addition of neutral salts. By reason of their indiffusibility, they may be separated from the diffusible crystalloid substances by dialyzers, such as vegetable parchment. This separation, however, cannot be accomplished without difficulty.

Considerable progress has been made in this direction more recently by the work of J. Loeb.¹ It has been shown that while non-ionized gelatin may exist in gelatin solutions on both sides of the isoelectric point (which equals an hydrogen ion concentration of $\text{CH} = 2.10^{-5}$ or $\text{pH} = 4.7$), gelatin when it ionizes, can only exist as an anion on the less acid side of its isoelectric point ($\text{pPH} > 4.7$) and as a cation only on the more acid side of its isoelectric point ($\text{pH} > 4.7$). At the isoelectric point gelatin can dissociate practically neither as anion nor cation.

On the acid side of the isoelectric point amphoteric electrolytes can only combine with the anions of neutral salts, on the less acid side of their isoelectric point with cations; and at the isoelectric point neither with the anion nor cation of a neutral salt. It has also been shown that the isoelectric point of an amphoteric electrolyte is not only a point where the physical properties of an ampholyte experience a sharp drop and become a minimum, but that it is also a turning point for the mode of chemical reactions of the ampholyte. It is suggested by Loeb that this chemical influence of the isoelectric point upon life phenomena overshadows its physical influence.

Surface-tension.—Another factor which no doubt plays a part in absorption is surface-tension. Its action may be illustrated by placing a drop of water upon an oily surface or by suspending a globule of oil in a fluid with which it does not readily mix. In either case, there is a tendency on the part of the drop to assume a spherical outline. This is brought about by the fact that its surface-layer is under a certain tension which tends to give to the whole as small a surface as possible, and naturally, the force here at work is cohesion, *i.e.*, a mutual attraction between its constituent molecules. Supposing that we single out a molecule in its interior, it will be found that this

¹ Jour. of Gen. Physiol., i, 1918, 39.

unit is acted upon from all sides by the neighboring molecules, and that this action is equal in all four directions. At the surface, on the other hand, conditions are different, because here the molecules are not counterbalanced by a tension resting upon their external surfaces. Hence, they are pulled inward. Now, it will be seen that if the drop is surrounded by some fluid, its surface-molecules must be acted upon by the molecules of the medium, depending, of course, upon the nature of the latter. Obviously, this now uneven balance must give a different shape to the drop as a whole. The surface-tension may also be altered by changes in temperature, because heat tends to separate the different molecules from one another and to counteract their power of attraction. Cold, on the other hand, increases the surface-tension, because it brings the molecules closer together by removing from them the kinetic energy necessary for expansion. A third means by which the surface-tension may be altered, is the electrical current.¹

Adsorption.—The phenomenon of adsorption may be illustrated by exposing a solid substance in powdered form to a solution of some kind. The dissolved substance then accumulates upon the surfaces of the solid particles and leaves the solution, thereby lessening the concentration of the latter. This property is well displayed by the colloids to which the proteins, with the exception of the peptones, belong. Consequently, since our body contains very extensive surfaces which lie in relation, on the one hand, with the body-fluids and, on the other, with nutritive material, most favorable conditions are established for the occurrence of this phenomenon.²

A. ABSORPTION FROM THE INTESTINAL CANAL

The Absorption of Water.—Water and the ordinary soluble salts are absorbed unchanged, but the quantity which actually finds its way into the body, depends upon the intake and how greatly the system is in need of it. Since water is lost constantly, because it serves as a medium for our secretions and excretions, correspondingly large quantities of it must be consumed in order to make up for this loss. In a way, therefore, it may be said that the body is in water-equilibrium, and it makes little difference whether a man takes in one liter or six, because any superfluity is soon compensated for by a greater discharge, chiefly through the kidneys. Quite similarly, any scarcity is equalized by a corresponding reduction in the quantity of the secretions and excretions. In the latter case, however, a physiological limit is soon reached, at which the phenomenon of tissue-thirst arises as a means of safety. The body also possesses the power of guarding itself against too large an intake, because unusually large

¹ Macallum, *Ergebn. der Physiol.*, xi, 1911, 598; also: Traube, *Pflüger's Archiv*, cv, 1904, 559.

² Hofmann, *Zentralbl. für Physiol.*, xxiv, 1910, 805; Robertson, *Jour. Biol. Chem.*, iv, 1908, 35; and Van Slyke, *ibid.*, iv, 1908, 259.

quantities of water give rise to mechanical reflexes, nausea, irritations of the gastric and intestinal mucosa, and certain symptoms associated with hydremic plethora.

One of the reasons for the relative ease with which the system may be surcharged with water is that the alimentary surface is not sufficiently resistant to counteract and to prevent osmosis. Moreover, while the excessive intake of water may eventually cause the feces in the large intestine to become watery, this channel offers a certain resistance to its escape which it avoids by passing through the epithelium. At least, this is the tendency in most persons. Thus, it is a matter of common experience that constipation is usually associated with a disinclination to take much water, and as much as 3 to 5 liters may be absorbed, before the feces actually assume a fluid consistency. The absorption of water is most intense in the small intestine, but some of it also passes over into the cecum, because in this segment the fluid ileac contents are gradually changed into the semi-solid feces. Under normal conditions the stomach does not allow an appreciable quantity of water to pass through, although slight amounts of peptones, sugar, and certain drugs may be absorbed from its cavity.¹ It is for this reason that stenosis of the pylorus and dilatation of the stomach are usually accompanied by tissue-thirst, which cannot be relieved by drinking. As far as the channel of absorption is concerned, it has been observed that the introduction of salt solutions into the small intestine does not increase the flow of lymph from the thoracic duct, whereas large quantities of water frequently bring about a dilution of the portal blood. It is probable, therefore, that these foodstuffs pass directly into the blood-stream and not into the lacteals and lymphatic system.

The osmotic interchanges between the intestinal contents and the blood, may be illustrated in the following manner. A section of the small intestine of an etherized mammal is drawn through a wound in the abdominal wall. Two loops of equal size are then marked off by three ligatures. Into one of these a quantity of normal saline solution is injected which thoroughly distends its walls. Into the other, a few drops of a concentrated solution of magnesium sulphate are injected. Having replaced these loops in their proper place in the abdominal cavity, the animal is allowed to rest for about one hour. At the end of this time, it will be found that the loop containing the saline solution, is now practically empty, while the formerly perfectly flabby loop containing the magnesium sulphate, is highly distended. This experiment clearly shows that the saline solution acts as a hypotonic solution, and the magnesium sulphate solution as a hypertonic solution. In the former case, water is removed from the intestinal canal, and in the latter, from the blood. This is the picture of saline catharsis, because the introduction of such solutions as citrate of mag-

¹ Moritz, *Zeitschr. für Biol.*, xlii, 1901, 565.

nesium, epsom salt, and others, causes large quantities of water to be poured into the intestinal canal which eventually excite peristalsis. Other cathartics, such as cascara sagrada, act by stimulating the peristalsis without rendering the feces especially watery, and still others, such as the inert oils, by lubricating the intestinal surfaces as well as the feces.

While the experiment just described, lays special emphasis upon osmosis, it may be shown that this factor is by no means the only one concerned in absorption. Thus, it will be remembered that the villi of the small intestine are supplied with capillaries in which the pressure cannot be less than 30 or 40 mm. Hg. Evidently, absorption takes place against this pressure. It has also been shown that if a certain quantity of the animal's own blood-serum is introduced into the intestine, its water and salts will be absorbed, while its proteins are left behind. Some time later, however, all of this serum is taken up and this in spite of the fact that the fluids on the two sides of the intestinal epithelium are practically identical. These and other experiments that might still be mentioned, prove very conclusively that the lining cells of the intestine are able to intervene in this process by virtue of certain forces which originate during their metabolism. This implies that the different substances do not simply pass through the pores in this membrane, but actually interact with the solvent as well as with the cytoplasm of these cells.

The Absorption of the Carbohydrates.—Since only the monosaccharides are readily dialyzable, the polysaccharides must first be converted into their simplest form. We have seen that this process involves a constant hydrolysis which is effected by the enzymes mentioned previously. In the intestine, therefore, we have such substances as dextrose, levulose or fructose, and galactose.

The first is present in largest amounts and is easily diffusible and reduced by the tissue cells. Such disaccharides as cane-sugar, milk-sugar, and maltose, are also soluble and diffusible, but cannot be converted directly into glycogen, nor can they be fully utilized by the tissue-cells. The small percentage of them actually made available to the latter, has previously been acted upon by the maltase of which a small amount is present in the body-fluids. The difference in the diffusibility of these sugars is also shown by the fact that as small an amount as 100 gm. of glucose when introduced into the intestine, may give rise to glycosuria, while as much as 300 gm. of cane-sugar may be ingested before the aforesaid symptom is produced. Lactose is absorbed with even greater difficulty and hence, this sugar must pass into the feces whenever lactase is present in insufficient amounts. The absorption of the simple sugars is effected chiefly in the small intestine, and the chief channel of absorption is the portal vein and not the lymphatic system.¹

¹ Munk, *Archiv für Physiol.*, 1890, 376.

The Absorption of the Fats.—In the upper small intestine the fats appear as glycerin and fatty acids, while in its lower segments some of these fatty acids have been combined with alkalies to form soaps. This implies that the neutral fat ingested is hydrolyzed by the gastric, pancreatic and intestinal juices, the end-products of this lipolysis being the substances just mentioned. We know that the alkaline soaps are soluble in water, while those of calcium and magnesium are soluble in bile. This is also true of the free fatty acids. Herein really lies the importance of bile as an aid to pancreatic digestion; *i.e.*, while it does not dissolve neutral fat, it possesses a powerful solvent action upon fatty acids and soaps and even upon the otherwise insoluble soaps. From this statement it may be gathered that this secretion is a prerequisite of the normal absorption of fat, because in its absence more than half of this foodstuff is lost to the body and escapes into the feces. It cannot surprise us to find that the accumulation of these masses of unutilized fat also seriously interferes with the digestion and absorption of the other foodstuffs. Similar conditions result in the absence of the pancreatic juice, but it seems that the loss of this secretion may be compensated for in a large measure by the secretions still remaining as well as by the activity of micro-organisms.¹

In its journey through the epithelial cells this material is then synthetized into neutral body-fat. The soaps are split, while the fatty acids thus liberated, are united with glycerin to form neutral fat under elimination of water. This fat is then diverted into the lacteals of the different villi, whence it reaches the mesenteric lymphatics and eventually the thoracic duct and venous circulation. It is true, however, that only about 60 per cent. of the 95 per cent. of the fat usually absorbed, can be accounted for in this way, whereas the other 40 per cent. must be transferred into the portal radicles directly or be burned up during their passage through the intestinal epithelium. In support of the former view might be mentioned the fact that from 32 to 48 per cent. of the fat enters the system in spite of the ligation of the thoracic duct. Obviously, this absorption can only take place through the portal terminals. As far as the time is concerned during which this transfer is accomplished, it might be stated that in the dog from 9 to 21 per cent. of the fat is absorbed within 3 to 4 hours, 21 to 46 per cent. in 7 hours, and the remaining portion in 18 hours.

At the height of absorption even the distalmost lymphatics are sharply outlined against the dark red background of the intestine by their milky white contents. Even the blood presents an oily appearance, owing to its admixture with chyle, and if a sample of this blood is allowed to clot, the serum derived therefrom exhibits a white color, and fat globules gradually collect upon its surface. This cannot surprise us, because fat absorption is both abundant as well as rapid,

¹ Leathes, "The Fats," Monographs in Biochem., Longmans, Green & Co., 1912, and Dakin, "Oxidations and Reductions in the Animal Body," *ibid.*, 1912.

as much as 12 grams of fat being absorbed by a dog of medium weight in the course of one hour. Histologically, it is of interest to note that the fat globules may be traced in their journey through the epithelial lining by virtue of the power of the unsaturated fatty acids to reduce osmic acid. When stained in this way they appear as dark granules of varying size within the cytoplasm of the different cells. It should be remembered, however, that this stain does not furnish a means of determining the actual amount of fat present within these cells, because only the free fatty acids are rendered visible thereby. On leaving these cells the fat globules enter the tributaries of the lacteals.¹ There is no reason to believe that they are transported into these channels by the leukocytes, as has been supposed by Schäfer and others. The histological picture just briefly described, has led many observers to conclude that the fat globules traverse the intestinal epithelium in their original form. This view constitutes the so-called *mechanistic theory* of fat absorption. As we have seen, the evidence now at hand shows that the fat is broken down and is reconstructed into neutral fat before it leaves the lining cells. This fact forms the basis of the *chemical theory* of fat absorption.

The Absorption of the Proteins.

—The proteins of the food are retained in the small intestine in the form of peptones and their amino-acid derivatives. The latter traverse the intestinal epithelium and are eventually converted into the proteins of the body. We know this to be true, because amino-acids may be isolated from the blood, and because animals may be kept in nitrogen-equilibrium by feeding them with completely predigested protein mixtures. It has also been observed that the introduction of foreign proteins and even of peptones into the circulation, gives rise to severe symptoms and may even result in the death of the animal. In other words, the direct introduction into the blood-stream of substances which are otherwise chemically indistinguishable from the digested proteins is usually followed by the development of anaphylactic reactions. These same substances given by mouth, are perfectly harmless. It appears, therefore, that the proteins cannot be absorbed as such from the intestine, but must first be reduced into

FIG. 521.—SECTION THROUGH THE LINING CELLS OF THE INTESTINE (RAT) AT DIFFERENT PERIODS AFTER THE INGESTION OF FAT.

¹ Whitehead, Am. Jour. of Physiol., xxv, 1910, 28, and Mendel, *ibid.*, xxiv, 1909, 493.

their amino-acids, from which the proteins of the body are then reconstructed. It is also evident that these products of protein digestion enter the portal radicles, because the composition of the lymph obtained from the thoracic duct, is not appreciably altered during protein absorption. Moreover, it has been shown that the ligation of this collecting channel does not interfere with the intake of proteins as determined by the output of urea.¹

These facts have led to the establishment of the hypothesis that the amino-acids are reconstructed into the proteins of the blood while they traverse the intestinal lining. But since this view is based upon negative evidence, and is contradicted by the presence of amino-acids in the blood, it cannot be retained in its original form. Instead, it must be concluded that a true synthesis of the amino-acids by the intestinal lining cells does not take place and that these bodies enter the blood directly. From this medium they are then picked up by the different cells either to replace the protein material which the latter have lost, or to be excreted directly.² The acceptance of this view makes it necessary for us to discard the assumption that the white blood corpuscles play a part in the transfer of these bodies from the lining cells into the blood-stream (Schäfer). Consequently, it may be concluded that the increase in the number of leukocytes after meals is caused in all probability by changes in the circulation.

The difficulties encountered in endeavoring to prove the presence of amino-acids in the blood, are dependent upon the fact that their absorption is effected very slowly and that they are diluted after that by large quantities of blood, and carried with greatest speed to the tissues. Consequently, they do not remain in the blood for any length of time, but are quickly acted upon by the tissue-cells. An additional difficulty is presented by the fact that their chemical isolation is seriously hampered by the presence in the blood of a large quantity of coagulable proteins.

In accordance with the above view, the amino-acids must be regarded as mere building stones which may be brought together selectively to form the body-proteins. This is also true of the amino-acids constituting the proteins of the food, because the differences which they show are really due to the manner in which their molecules are combined. As soon as the protein material has been split by the action of the successive proteolytic enzymes, their amino constituents are again united in the organism in accordance with the peculiar requirements of the tissue-cells. In this way, a large number of perfectly new combinations may be produced. It must also be considered as an established fact that the intestinal cells possess the power of splitting the amino groups from those polypeptides which have been swept into them. This deduction is based upon the fact that the intestinal

¹ Folin and Denis, *Jour. Biol. Chem.*, xi, 1912, 493.

² Paton and Goodall, *Jour. of Physiol.*, xxxiii, 1915, 20, also Burian and Schur, *Wiener. klin. Wochenschr.*, 1897.

mucosa contains more ammonia than any other tissue, and that the blood of the mesenteric veins contains from 6 to 10 times as much ammonia as that of other veins.

In man practically all the proteins are taken in as insoluble compounds, or are rendered so by the process of cooking. Their absorption, therefore, necessitates their first being brought into solution and this end is attained by hydration and the action of the different proteolytic enzymes. Certain evidence is also at hand to show that a certain proportion of the protein may be absorbed before it has actually reached its final stage of cleavage. Thus, it has been mentioned above that the proteins of blood-serum are eventually taken up; in fact, Friedländer states that as much as 21 per cent. of white of egg may be absorbed by washed small intestine in the course of three hours. Syntonin and casein, on the other hand, are not absorbed. Furthermore, patients fed per rectum with protein material, are capable of absorbing a considerable portion of it, although proteolytic enzymes are not present in this segment of the intestine. It is also a matter of common experience that certain persons may develop an idiosyncrasy or anaphylaxis against the proteins of milk and white of egg, which is due in all probability to the absorption of protein in its more complex form. We are justified, however, in concluding that, under perfectly normal conditions, the absorption of only partially reduced protein is the exception.

Besides the increase in the number of the leukocytes, it has been noted by Reuter that the cells of the villi become swollen when protein absorption is going on. Furthermore, their cytoplasm does not stain deeply at this time, owing, in all probability, to the accumulation of a hyaline coagulable material.

B. ABSORPTION FROM THE CAVITIES OF THE BODY

Absorption from the Peritoneal Cavity.—In the intestine, the body-fluids are separated from the liquefied foodstuffs by a layer of columnar epithelium which owing to its depth, is capable of influencing diffusion in an active manner. The body-cavities, on the other hand, are lined with only a thin sheet of endothelial cells, and hence, we might expect in this case a preponderance of the physical forces. While these functional differences no doubt exist, the fact still remains that the endothelial cells are by no means perfectly passive entities. We have really come to this conclusion on previous occasions, while discussing the part played by the glomerulus in the formation of urine and the function of the endothelium of the blood capillaries in the production of lymph. As far as the lining of the pleural and peritoneal cavities is concerned, it has been noted repeatedly that pleural and ascitic effusions may be reabsorbed in the course of time, provided the cause leading to these extravasations has ceased being active.

This is also true of blood-serum and isotonic salt solutions when introduced into these spaces.

In general, it may be said that the endothelium acts in the same manner as other animal membranes. Thus, it has been shown by Roth¹ that the introduction of hypotonic salt solutions into the peritoneal cavity leads to a rapid absorption of its water until it has become isosmotic with the blood. Eventually, all of the solution disappears from this cavity. A hypertonic salt solution, on the other hand, first draws water from the blood until an isosmotic condition has been established. The fluid as a whole then begins to pass over into the system. It is difficult to explain these phenomena unless we assume with Recklinghausen² that the peritoneal cavity stands in direct communication with the lymphatic system by means of minute defects or stomata which are situated between the individual endothelial plates. Thus, while the ordinary laws of diffusion would play the most important part to begin with, the final escape of the fluid would occur through these openings. This explanation has much in its favor and especially since this absorption is proportional to the pressure under which the fluid is injected into the cavity. But inasmuch as the aforesaid stomata have not been definitely recognized by histologists, Starling³ has supposed that the absorption from these cavities is dependent upon the fact that the proteins of the blood are indiffusible and exert, therefore, a considerable osmotic pressure upon the neighboring salt solution. This explanation is strengthened by the fact that the absorbed material enters the blood and not the lymph, because the ligation of the thoracic duct does not impede this process. Obviously, this subject is still in a decidedly theoretical state and we cannot do much else at the present time than to consider it in the same light as the formation of the lymph, *i.e.*, we must suppose, and rightly so, that the purely physical factors of diffusion and osmosis are modified by the metabolic activity of the endothelial cells.

Absorption Through the Skin.—It has been stated in one of the preceding chapters that the skin excretes carbon dioxid, water, salts and at times also urea.⁴ To what extent the skin may also be regarded as an organ of absorption has not been definitely ascertained, although it may be assumed that this function must differ in different animals. Concerning the skin of man it has been established that it possesses practically no absorbing power under ordinary conditions, whereas that of the frogs and eels (not the fish) absorbs oxygen as well as water, alcohol, and possibly also salts and other substances.⁵

¹ Engelmann's Archiv., 1899.

² Virchow's Archiv, xxvi, 72; also: Meltzer, Jour. of Physiol., xxii, 1898, 196.

³ Jour. of Physiol., xviii, 1895, 106.

⁴ Schierbeck, Archiv für Physiol., 1893, and Taylor, Jour. Biol. Chem., ix, 1911, 21.

⁵ Berg, Dissertation, Dorpat, 1868, Bohr. Skand. Archiv für Physiol., x, 1900, 88, and Maxwell, Am. Jour. of Physiol., xxxii, 1913, 286.

C. THE FORMATION OF THE FECES

Character of the Feces.—The feces are alkaline in their reaction, and contain the indigestible constituents of the food plus a very small proportion of nutritive material which has escaped digestion, epithelial cells, pigment, mucin, and countless bacteria. The products of bacterial decomposition, include indol and scatol to which their disagreeable odor is due, and also certain gases, such as NH_4 , CO_2 , H_2 , N and H_2S . A small quantity of fecal material is also excreted during periods of starvation, as well as from isolated loops of intestine. In the latter case, however, it consists solely of desquamated epithelium, intestinal juice, and bacteria; simulating, therefore, the meconium of the new-born child which embraces solely concentrated bile and cast-off epithelium. The character of the feces of a normal adult depends in a large measure upon the type of the food ingested. They contain elastic fibers, and the remnants of the connective tissues, spiral vessels of plants, and vegetable residue in the form of cellulose. When no vegetables have been ingested, about 65 to 75 per cent. of the feces consist of water, while their dry residue contains about 7 per cent. of nitrogenous material. Their non-nitrogenous portion is composed of about 11 to 12 per cent. of ash and 12 to 18 per cent. of substances soluble in ether, as well as of sterobilin and other bile residues. The ethereal extract embraces fatty acids, cholesterol, a small amount of lecithin, and neutral fat. The proteins consist of mucin and nucleoprotein, derived from the epithelial cells and the countless numbers of bacteria. The ash embodies chiefly calcium phosphate and small amounts of iron and magnesium.

Very different conditions are met with if the diet contains large amounts of cellulose, because this material escapes from the small intestine unchanged and may carry other substances with it. In the large intestine, it is first acted upon in a slight measure by bacteria before it actually becomes a constituent of the feces. Thus, Voit has shown that as much as 42 per cent. of the nitrogen of the food of vegetarians may be lost to the system, obviously because the digestive juices cannot penetrate its cellulose investments. Only about 85 per cent. of the dry substance of green vegetables is available for absorption, and only 80 per cent. of carrots and turnips. But naturally, the vegetable proteins as such are as digestible as the animal proteins, and their complete utilization requires merely maceration and cooking to free them from the cellulose. In the herbivora, of course, conditions are quite different, because in them the beginning portion of the large intestine is set aside especially for the digestion by fermentation of these particular types of foods. This material may remain here for two or three days, while it undergoes slow reduction and absorption.

Botulism.—Excessive protein putrefaction in the intestine may give rise to a complex of symptoms, consisting of constipation, vertigo, diplopia, hemianopia, difficulty in swallowing, weakness, and cardiac

irregularities. In most instances, these symptoms are attributable to an unusual inactivity on the part of the large intestine or to the ingestion of smoked and canned meat and other foods. It is said that these toxins are derived from processes instigated by the *Bacillus botulinus*, an anærobe which is easily destroyed by the cooking of the food.

The Formation of the Feces.—Even at the height of digestion the small intestine is not distended with food, but contains merely froth and semi-solid masses of mucous material which are never large enough to separate its walls very widely. Hence, the name of jejunum or “empty gut.” This peculiar condition finds its origin in the periodic entrance of chyme and its relatively rapid distribution through a large stretch of intestine. At the ileocecal valve a certain quantity of its water has already been abstracted from this material, although enough of it is left behind to give to the contents of the cecum the consistency of a thick broth. The regular and antiperistaltic movements of this segment, together with those of the ascending colon, then allow sufficient time for most of this water to be absorbed, so that the transverse colon receives this material in a more compact and dry form. Obviously, any retardation of the feces must tend to increase this absorption of water, permitting them to become more firmly lodged in the haustral spaces, whence they are dislodged only with difficulty. In extreme cases of constipation even the descending colon may become blocked with these impacted masses, which then set up disturbing reflexes by virtue of their irritating action upon the intestinal mucosa and neighboring abdominal organs.

While it is not my intention to enter into a lengthy discussion of the causes and effects of intestinal stasis and constipation, it might be mentioned that the ingestion of food containing a larger proportion of vegetables may obviate this difficulty, because it tends to shorten the time consumed in the passage of the food through the intestine. This result it accomplishes first by virtue of its greater content in water, and secondly, by means of its stimulating influence upon peristalsis. Consequently, the indigestible cellulose of the food is not without value, because it increases the bulk of the feces and sets up certain mechanical reactions, which lead to a quicker evacuation of the large intestine. This point is more fully illustrated by the fact that an ordinary mixed diet gives rise to a daily output of feces consisting of about 100 grm. of water and 35 grm. of solids, whereas a vegetable diet yields 260 grm. of water and 75 grm. of solids.

CHAPTER LXXXVI

THE HISTORY OF THE DIFFERENT FOODSTUFFS
IN THE BODY

General Discussion.—The process of alimentation having been completed by the absorption of the foodstuffs, the latter circulate in the blood and are then acted upon by the cells of the different tissues. One of two things may now happen to them, namely, they may be taken up to form an intricate part of the tissue-substance or may be burned up immediately and excreted. Eventually, of course, even the first portion must again be discharged by the cells into the circulating media, because activity entails a constant loss of substance. As far as excretion is concerned, it is, therefore, quite immaterial whether a given foodstuff first becomes an actual part of a cell or does not, because both portions are finally turned into waste products. Clearly, every living entity attains at a particular time of its life a mature size which it retains for some time by properly balancing its outgo in waste material by an adequate ingo of nutritive substances. Meanwhile its physiological destiny is to produce energy in its various forms, simulating a steam engine which converts its fuel into waste under an evolution of energy. In order to satisfy its wants; to retain its weight; and to enable it to yield energy, the living substance requires fresh air, drink and food. Only when each of these three things is supplied to it can it continue incessantly to oxidize and to produce work. Thus, each cell may be said to be in a state of unstable equilibrium which favors the building up processes during its period of growth and the tearing down processes during its period of decline.

While cellular anabolism and catabolism in this general form is not difficult to understand, it is true that we are not as yet in a satisfactory position to follow the different foodstuffs in their journey through the body with exactness. The reason for this lies in the extreme complexity and invisibility of the intracellular processes. Regarded in a general way, it may be said that the body consists of 64 per cent. of water, 16 per cent. of proteins, 14 per cent. of fat, 5 per cent. of salt, and 1 per cent. of carbohydrates. Among its constituents might be mentioned carbon, nitrogen, hydrogen, oxygen, sulphur, phosphorus, fluorin, chlorin, iodin, sodium, potassium, calcium, silicon, magnesium, lithium, iron, and at times also traces of manganese, copper and lead. Excepting oxygen, nitrogen and hydrogen, these elements

are usually united into compounds, forming (a) the mineral or inorganic constituents, and (b) the organic constituents of our body. Physiological chemistry concerns itself chiefly with the latter which present themselves as carbohydrates, fats and proteins. So far, however, chemical analyses have not succeeded in establishing anything further regarding the "life history" of these substances than what might be termed a balance sheet between their ingo and outgo. This need not surprise us, because even the simplest determinations frequently necessitate difficult analytical procedures. In general, it may be said that our knowledge regarding the sum total of the changes which the foodstuffs undergo in our body (metabolism) has been derived from determinations of:

- (a) the quantity and quality of food ingested,
- (b) the quantity and quality of the material excreted,
- (c) the weight of the animal before and after the experiment, and
- (d) the energy evolved by the animal in the form of work and heat, while in the calorimeter.

THE METABOLISM OF THE CARBOHYDRATES

The Formation of Glycogen.—The animal derives its carbohydrates in the main from vegetable carbohydrates which upon digestion yield three monosaccharides, namely, glucose, fructose and galactose. About 500 grm. of carbohydrate are ordinarily ingested in the course of a day. Our body, however, is normally unable to synthesize this foodstuff, differing in this regard very sharply from the plants, which are able with the help of the chlorophyll to form a simple carbohydrate, probably formic aldehyde, from carbon dioxid and water. By condensation this simple substance is then changed into sugar, and eventually into starch. Since the aforesaid sugars are easily interconvertible, the tissues may form whatever type of sugar they need. This is true, for example, of lactose, a constituent of the secretion of the mammary glands, and of the galactosides of nervous tissue. Since lactose is a compound of glucose and galactose, it requires only a very slight intermolecular rearrangement to produce this substance. In other words, there is sufficient evidence at hand to show that one type of sugar may be transformed into another either by the cells of all the tissues or only by those of certain tissues.

It has been ascertained by Cl. Bernard (1853) that the sugar absorbed is not passed directly into the circulation, because the amount of reducing sugar present in the blood retains the almost constant value of 0.1 to 0.15 per cent. even at the height of digestion. In between the successive periods of absorption the percentage of this substance in the blood of the portal vein is about the same as that of the blood in the systemic channels, whereas during absorption the

sugar-content of the former is markedly raised.¹ These facts immediately suggest that some barrier is interposed which prevents the newly absorbed sugar from entering the general circulation. This conclusion is also upheld by the fact that extracts of the livers of animals which had been killed some time beforehand, contained a large quantity of reducing sugar, while those of washed livers exhibited an opalescence which was proved to be caused by the presence of a polysaccharide, known as *glycogen* ($C_6H_{10}O_{5n}$). When an extract of this kind is treated with alcohol, it yields an abundant precipitate which may be converted into sugar by hydrolysis with a mineral acid. This conversion also takes place in pieces of liver which have been allowed to stand for some time, so that their yield of glycogen gradually becomes less, while their content in glucose increases. In either case, this *glycogenolysis* proves that the hepatic cells must contain some enzyme which is capable of effecting this transformation. The name of *glycogenase* has been applied to it.

After an abundant intake of carbohydrates glycogen may be present in the liver in as large amounts as 12 per cent. of the weight of the fresh organ. It is demonstrable here in the form of hyalin chips which give a characteristic port-wine color with iodine; moreover, a liver of this kind is large, soft and easily injured. But while the chief source of glycogen is the assimilable carbohydrate material of the food, namely, glucose, fructose, galactose and mannose, it may also be formed from proteins or the products of their decomposition. Whether this conversion takes place under normal conditions cannot be stated with certainty, although it is known that a starving animal may employ this means to retain a certain store of sugar. Thus, it will be found that the liver of an animal during starvation contains only a very small amount of glycogen, whereas its blood sugar, although less than normal, has not disappeared altogether. This remnant of liver-glycogen, however, may be removed without difficulty by supplementing the starvation with muscular work. Inasmuch as no carbohydrates are ingested during this period, and inasmuch as the glycogen of the liver and muscles has been used up, it is evident that some sugar, or a substance similar to it, must have been formed from the proteins. This deduction seems justified, because no evidence has been presented as yet to show that glycogen may also be derived from the fats. Further, if an animal whose store in glycogen has been exhausted, is fed with washed fibrin, caseinogen, or even amino-acids, the liver will be found to have acquired glycogen. This substance also quickly disappears if the starving animal is thrown into convulsions by means of strychnin. If these spasms are stopped later on by the administration of chloral, a certain amount of glycogen is again found in the liver, derived in all probability from the tissue proteins.

¹ McLeod and Fulk, Am. Jour. of Physiol., xlii, 1917, 193, and Dakin, Oxidation and reduction in the animal body, Monogr. in Biochem., 1912.

Our search for the possible source of this glycogen leads us first of all to mucin, which yields a considerable amount of carbohydrate, but this substance does not play a significant part in metabolism. Contrariwise, it has been proved that casein, which does not contain a carbohydrate radicle, may be made to yield sugar when fed to animals suffering from phloridzin glycosuria. Similar tests with different amino-acids have given positive and negative results, although their composition does not vary very considerably. Two of these, however, have been proved to yield sugar, namely, alamin and aspartic acid. In the former instance this conversion is not difficult chemically, because the substitution of HO in its molecule for NH_2 gives lactic acid, from which sugar may be obtained without much difficulty. Quite similarly, if aspartic acid loses carbon dioxid, it is transformed into lactic acid. Another substance, the conversion of which into carbohydrate does not seem improbable, is glycerol. It may be concluded, therefore, that the body possesses the power of forming its sugar from the aforesaid substances, and possibly also from other amino-acids, although the chemistry of their conversion is not so obvious as in the cases just cited. Under ordinary circumstances, however, the body derives its glycogen directly from the carbohydrates of the food.

The Utilization of Sugar.—In the cells of the liver a twofold process is going on, namely, a conversion of the sugar into glycogen, and a reconversion of this polysaccharide into circulating sugar under the influence of an enzyme. We have seen that this circulating sugar is changed in the pancreas into a form (colloid) which is more acceptable to the tissue cells, *i.e.*, one which they can burn up more readily than ordinary glucose. Consequently, the glycogen of the liver serves as a reserve material which is deposited here temporarily as an inert polysaccharide. But the liver is not the only storehouse of sugar, because it is also found in abundant amounts in the muscle tissue. The difference between these two stores seems to be one of availability, because if a muscle is suddenly called upon to do extra work, it cannot await the transfer of sugar from the liver. It is for this reason that rapidly growing tissues invariably contain much glycogen which they make use of in the course of their subsequent development. Thus, while sugar is normally released by the liver into the blood stream, the outlying depots are there for the purpose of serving the more immediate needs of the body.

It is a well-known fact that every contraction of muscle, whether in the body or outside of it, consumes glucose. Thus, the normally contracting heart necessitates about 4 mgr. of this substance per gram of tissue in the course of 1 hour.¹ Now, since the muscle tissue forms about 42 per cent. of the body weight, its requirements in sugar must be considerable. Moreover, since our body contains only 1.0 per cent. of carbohydrates, it will be seen that this foodstuff, contrary

¹ Starling and Knowlton, Jour. of Physiol., xlv, 1912, 146.

to the proteins, does not serve as a permanent building stone, but merely as a temporary acquisition which is destined to yield energy.

Work and heat are derived in largest amounts from the muscles, and we have seen that their contractions require the presence of glycogen and sugar, and that each gram of sugar furnishes as much as four calories of the latter form of energy. Considering the preponderating mass of muscle-tissue and the high heat-value of sugar, it may, therefore, be concluded that the oxidation of this substance constitutes a safety mechanism by means of which the body is enabled to protect its real building stones, the proteins. Fat plays a similar rôle, but we shall see later on that it occupies an intermediate position and serves merely as an accessory means of safeguarding the protein substratum of the body. Thus, an animal may be retained in nitrogen-equilibrium if it continues to ingest a small amount of protein material to make up its ordinary loss in tissue-proteins, and if it continues to take in a sufficient quantity of carbohydrates (or fats) to make up for the energy requirements of the body. Inasmuch as the carbohydrates merely play the part of oxidizing substances and spacers of the tissue-proteins, it will be seen that they alone cannot keep the body in nitrogen-equilibrium. Consequently, an animal fed exclusively on carbohydrate food must eventually lose its tissue-proteins, and starve to death in spite of its abundant intake of carbohydrates. On the other hand, if an animal is in nitrogen-equilibrium to begin with, the abundant ingestion of carbohydrates first gives rise to a storage of glycogen and subsequently to a synthesis of the superfluous sugar into fat. The latter is held in reserve as an accessory substance to be employed for future oxidations. This "carbohydrate-fat" differs somewhat in its consistency from the ordinary tissue-fat.

The final product of the oxidation of sugar is carbon dioxid and water, and its principal excretory channel the lungs. Thus, we find that the increased output of energy which accompanies muscular exercise is characterized by a greater outgo of carbon dioxid and a greater consumption of oxygen. This respiratory change immediately suggests an increased metabolism of the carbohydrates and fats. But, while the final stage of the oxidation of the carbohydrates is quite evident, much diversity of opinion prevails regarding the intermediary transformations of this foodstuff. The initial change is a hydrolytic cleavage which liberates some chemical energy, and the final stage an oxidation and evolution of that large amount of energy, which after all is the purpose of the reduction of this foodstuff. As an intermediary stage is usually mentioned the production of lactic acid, through the preliminary formation of glyceric aldehyde and methylglyoxal. It has been shown that lactic acid is present in the body chiefly as the dextro-rotatory variety or sarcolactic acid, and as the optically inactive variety. Whether all of this lactic acid is derived from the sugars is still in doubt, although it must be admitted that this is its principal source.

The Regulation of the Sugar Supply of the Body.—The sugar content of the blood of the general circulatory system is determined by two factors, namely, by the production of glucose by the liver (glycogenolysis), and by the consumption of this substance by the tissues (glycolysis). Both these processes are in turn dependent upon an adequate conversion of the absorbed sugar into glycogen (glycogenesis). Consequently, it may be said that the sugar content of the body is the result of an interaction between these three factors, and that such conditions as hyperglycemia and glycosuria are the outcome of a disturbance in any one or several of these processes.¹ Under normal conditions, a harmonious interaction between these factors may be brought about through the nervous system or through chemical agents contained in the blood stream. Regarding the nervous control we have the positive evidence of Cl. Bernard that a puncture of the floor of the fourth ventricle (rabbits) is usually followed by an excessive secretion of urine, containing abnormally large amounts of sugar (glycosuria). This has led to the assumption that the aforesaid activities are under the control of a special center which is often referred to as the *glycogenic or diabetic center*.

It has been shown that the stimulation of either the greater splanchnic nerves or the hepatic plexus gives rise to glycosuria, the claim being made that these nerves are concerned with the storage and conversion of glycogen by the cells of the liver. It is held further that this regulation is under the control of a hormone secreted by the adrenal glands, but the evidence so far presented in support of this contention, is not at all convincing. In spite of this fact, however, it cannot be doubted that glycosuria is frequently associated with mental excitement. Furthermore, the disease of diabetes mellitus usually affects persons with neurotic tendencies or those who are under a constant and severe mental strain, or whose work demands much mental concentration and exactitude.² At present, however, no facts are at hand to show that diabetes mellitus finds its initial cause in an outpouring of adrenin in consequence of too frequently repeated emotions, such as anger, fear and fright.³

The control of the formation and consumption of the sugars by hormones may be discussed at this time in a very brief manner, because this subject matter has already been dealt with in a preceding chapter. McLeod¹ states that this regulation may arise in consequence of (a) the concentration of the glucose in the blood, (b) the presence in the blood of the products of decomposition of the glucose, and (c) the action of some internal secretion. In accordance with this investigator, the first possibility is based upon the law of mass action, in

¹ McLeod, *Physiol. and Biochem. in Modern Medicine*, C. V. Mosby, St. Louis, 1918; and Hewlett, *Monogr. Med.*, Appleton and Co., 1917.

² Cannon, *Bodily Changes in Pain, Hunger, Fear and Rage*, Appleton and Co., 1915.

³ Allen, *Glycosuria and Diabetes*, Boston, 1913; also: Von Noorden, *Metabolism and Pract. Medicine*, Chicago, 1907.

agreement with which the conversion of the glucose into glycogen, as well as the conversion of the latter into the former substance, is determined by the amounts of glucose in the blood available for purposes of oxidation. It cannot be doubted that this process is actually at work, but obviously, the fact that it takes place does not offer an explanation for the manner in which it is accomplished. The second possibility finds its basis in the fact that such products as lactic acid and carbon dioxid are circulating in the blood and change the hydrogen ion concentration of the blood, thereby exciting a glycogenolysis. The third possibility, that this regulation is effected by means of a hormone secreted by some ductless gland, possesses a sound experimental basis. Chief among these internal secretory organs is the pancreas, then follow the adrenals, parathyroids and pituitary.

We have previously noted that the hyperglycemia and glycosuria, following the removal of the pancreas, are due to the loss of an internal agent which makes the sugar immediately available for oxidation by the tissue cells. The other glands, in all probability, act in an indirect way through the nervous system, increasing glycogenolysis. These two conditions, therefore, would give rise to the so-called *pancreatic* and *hepatic* types of glycosuria. The temporary *alimentary* type is, of course, dependent upon an increased absorption of sugar and an overburdening of the system with this substance. A fourth method of producing glycosuria has been discovered by Mering.¹ It has been used extensively by Lusk,² and consists in the administration of a glucoside, known as phloridzin, which is derived from the bark of the roots of the apple, cherry and pear trees. It produces a glycosuria in spite of the fact that the sugar content of the blood may be below normal. This shows that this type of glycosuria must be due primarily to a leakage of the sugar through the kidneys in consequence of an injurious action of this substance upon the renal epithelium. Phloridzin-glycosuria, therefore, is a type of *renal glycosuria*. The temporary glycosuria which may be developed in consequence of nervous excitement is in all probability to be classified as a disorder of glyco-genesis and glycogenolysis.

It will now be seen that the condition of *acidosis* cannot be attributed exclusively to a disarrangement of the carbohydrate metabolism, because the bodies causing this disturbance are aceto-acetic and β -oxybutyric acid, which are the oxidation products of acetone and the fatty acids. When these substances accumulate in the course of diabetes mellitus, the condition is known as *ketosis*. It appears to be due to the fact that the fats cannot be burned up thoroughly unless their combustion is stimulated by the heat derived from oxidizing sugar. In the absence of this heat, the fats are imperfectly reduced. Conse-

¹ Verhandl. des Kongr. für inn. Medizin, vi, 1887, and Zeitschr. für klin. Med., 1889.

² Zeitschr. für Biol., xlii, 1904, 31.

quently, ketosis is caused by an imperfect balance between the metabolism of the fats and carbohydrates.¹

A term frequently met with in the literature upon carbohydrate metabolism is the *D:N ratio*. We have seen that the absolute withdrawal of carbohydrate from a diabetic animal does not prevent the excretion of sugar in its urine. Since this dextrose is not derived from the fats, it must be synthesized from the proteins. Minkowski and Lusk² have shown that a dog in complete glucose intolerance may form as much as 60 gm. of glucose. Now, inasmuch as 100 gm. of proteins yield about 16 gm. of nitrogen in the urine, the ratio of dextrose to nitrogen would be $60:16 = 3.7$. Lusk states that a *D:N* ratio varying between 3.3 and 3.7 is a fatal ratio, because it proves that a person kept on a diet which is free from carbohydrate, cannot consume sugar.

THE METABOLISM OF THE FATS

The Source of the Body Fat.—The neutral fats formed by a resynthesis of the fatty acid and glycerin in the lining cells of the intestine, find their way into the lacteals, whence they reach the blood stream by way of the thoracic duct. But since the fat content of the blood of the portal vein is invariably higher than that of the external jugular, it is claimed by some investigators that a slight amount of fat also enters the intestinal capillaries directly. As far as the systemic blood is concerned, it has been found that its content in fat (0.7 per cent.) remains tolerably constant, provided only moderate amounts of fat are ingested. The intake of larger quantities of fat, on the other hand, invariably raises its percentage, which reaches its maximal value about 6 hours after a meal and then gradually declines to the twelfth hour. But since even the intravenous injection of oil emulsions does not lastingly increase the fat content of the blood, it must be concluded that the body possesses the power of storing this fat very rapidly, possibly in the liver. Even during starvation the blood-fat remains rather constant, proving thereby that the fat is being transported from the different depots to the starving tissues.

In the animal body the fats are usually deposited as the triglycerides of the different fatty acids, those of adipose tissue consisting of stearic, palmitic and oleic acids. Cow's milk also contains these acids, but in addition, also the esters of butyric and caproic acids and small amounts of caprylic, capric, lauric and myristic acids. Lard is made up in considerable part of the glycerides of the more unsaturated fatty acids, such as those of linoleic acid. It is evident, therefore, that the composition of the fat differs even in one and the same animal, and may in addition be varied by changing the food. This fact proves first of all that the epithelial cells of the intestine do not merely resynthesize the glycerol and fatty acids, but possess the power of forming their

¹ Woodyatt, Jour. Am. Med. Assoc., lxvi, 1916.

² Science of Nutrition, W. B. Saunders Co., 1912.

own particular kind of chyle fat. Very similar modifications must also be effected by the tissue cells themselves, because the fats are in all probability rehydrolyzed here, to become at least in part important constituents of the protoplasm. This deduction is in no way refuted by the fact that starving animals, when fed on foreign fat, are capable of storing this substance practically unaltered. This merely proves that it can be utilized in this form. Thus, Munk¹ has shown that an animal fed on colza oil, deposits fat from which erucic acid may be obtained, this acid being the basis of the glyceride contained in that oil. In a similar way, it has been demonstrated by Lebedeff² that the feeding of linseed oil or mutton fat to different dogs gives rise to a deposition of body fat which is characterized by a different melting point; that derived from mutton suet remaining solid at 50° C. Furthermore, Liebig has pointed out that the fats of different animals present certain peculiarities in their appearance, consistency, melting point, and general chemical properties, and are in turn different from the fat ordinarily ingested with the food. In fact, many animals, such as the herbivora, do not eat fat, although they often acquire a considerable amount of body fat. But this is really an old established fact, and has been used scientifically by Larves and G. Wert in their feeding experiments upon pigs.

These data have led in the course of time to various theories regarding the origin of the body fat. The modern view, which has been placed upon a solid experimental basis by Pflüger,³ holds that it originates in part from the fat and in part from the carbohydrate of the food. But the possibility that fat may also be derived from proteins, cannot be excluded, because since the latter are deaminized and converted into sugar and glycogen, these products may in turn be transformed into fat. The proteins, however, cannot form an important source of fat under ordinary conditions, because they constitute a relatively small portion of the daily ingesta.

While it cannot be stated definitely which of the first two sources is the more important, the fat of the food is no doubt the chief element in the carnivora, and the carbohydrate in the herbivora. Man, in all probability, makes considerable use of the carbohydrates, because they are really more easily reduced than the fats. Beyond this mere fact, little is known regarding the manner in which this conversion is accomplished. It involves, of course, a change of oxygen-rich sugar into oxygen-poor fat. Thus, if this process may be illustrated with stearic acid, it will be found that three molecules of glucose ($C_6H_{12}O_6$) give stearic acid ($C_{18}H_{36}O_2$) under an evolution of 16 atoms of oxygen. The fact that such a transformation gives rise to a liberation of oxygen is shown by animals who are depositing fat on carbohydrate food.

Their respiratory quotient, $\frac{CO_2}{O_2}$, is increased considerably, because

¹ Virchow's Archiv, xcv, 1884, 407.

² Centralbl. für die med. Wissensch., 1881.

³ Pflüger's Archiv, lxxvii, 1899, 521.

some of this oxygen will be made available for other oxidations, so that the animal need not take in so large an amount by respiration. In addition to this process of deoxidation, other changes are effected, such as the reduction of glucose into two molecules of lactic acid which in turn is converted into aldehyde and formic acid. By polymerization, the aldehyde may then be changed into aldol which yields butyric acid on oxidation or by transposition of its oxygen.¹

The Utilization of the Fats.—The final product of the metabolism of the fats is carbon dioxid and water, and their chief function to supply energy. This being the case, the body holds a considerable portion of this substance in reserve as a deposit in its different storehouses. Among the latter might be mentioned the liver, the tissues, and such special structures as the panniculus adiposus in the deep skin, the omentum, and retroperitoneal spaces. Any excess is stored in these places to be drawn upon later on when needed. Thus, fat serves as an additional protection to the proteins, being itself safeguarded by the carbohydrates. It presents, however, different characteristics in accordance with its origin and place of deposition. The ordinary depot-fat, for example, yields 95 per cent. of its total weight as fatty acids, while the tissue-fat yields only 60 per cent. This might imply that the former is neutral fat, while the latter is combined into lecithin and phospholipins. In the liver, the character of the fat varies with the intensity of the metabolism of this organ, being more like the fat of the tissue during its periods of relative quiescence and more like that of depot-fat during its periods of activity. It is also apparent that the amount of fat which may be stored in this way is almost unlimited, contrary to glycogen which at best cannot be stored in much greater quantities than 300 gm., *i.e.*, 150 gm. in the liver and 150 gm. in the muscles and other tissues.

This depot-fat is mobilized and transported to the active tissue whenever the latter has used up its own store of energy-yielding material, and obviously, this mobilization necessitates its conversion into fatty acids and glycerin, which products again give rise to neutral fat in the blood. No doubt, the chief seat of these oxidations is the muscle-tissue itself, and principally the cardiac and skeletal muscles. In the former, for example, enough fat is stored up to last for 6 or 7 hours. The intake then being insufficient to cover the outgo, all the available stored fat is drawn upon. Thus, a starving animal first exhausts its relatively small store of glycogen and then its depot-fat to the extent of 90 per cent. of the energy required. Consequently, a fat animal is able to survive complete abstinence from food much longer than a lean one. Besides this important function as a source of energy, the body-fat also serves as a factor in regulating the body-temperature by preventing an undue heat-dissipation, and lastly, as a factor in protecting delicate structures from mechanical injury.

The question whether the liver possesses a special influence upon

¹ Leathes, *The Fats*, Monogr. in Bioch., Longmans, Green and Co., 1912.

the metabolism of the fats, cannot be decided at this time. It is evident that this organ may absorb a considerable proportion of its fat directly from the portal blood. Thus, Raper¹ has shown that as much as 30 per cent. of coconut introduced in the intestine, may be recovered from the liver. The same is true of unsaturated oils, such as cod-liver oil and other fish oils. This probably accounts for their greater nutritive value. In addition, it has been shown that the liver possesses the power of desaturating fat, which may render it more easily reducible than saturated fatty acid. But, inasmuch as this organ also aids in synthesizing fatty acid radicals into the complex molecule of lecithin, it is entirely probable that this desaturation constitutes a preliminary step in this process of building up lecithin. While this substance is made up of glycerin, fatty acids, glyceryl-phosphoric acid, and a nitrogenous base cholin, it also seems to contain admixtures of proteins or carbohydrates.

Fatty Degeneration. Obesity.—Under abnormal conditions, the cells of such organs as the liver, heart, and kidneys may undergo degenerative changes which make them appear as if filled with extremely fine globules of fat. This is a common result of poisoning with phosphorus, arsenic or antimony. Although formerly believed to be due to a conversion of the proteins of the cytoplasm into a fat-like substance, fatty degeneration is now known to be caused either by an infiltration of the cells with fat transported from elsewhere or by a transformation of the molecular fat of the cells into a different variety of it. For this reason, it cannot be said that a fatty degenerated cell contains a greater amount of fat than it did normally; in fact, in many instances the reverse relationship holds true. Lusk, however, has shown that these poisons also interfere with the metabolism of the proteins in an indirect way by favoring the conversion of the carbohydrate-like radicle of the proteins into leucine and tyrosine, necessitating for this reason an increased consumption of protein.

Obesity signifies a disproportion between the total mass of the body and that made up of fat. This condition is caused by an excessive deposition of fat within the different depots of the body, giving rise to changes in the contours of the latter and various interferences with its normal activities and movements. In many instances, however, it is difficult to say just where the abnormal begins, because animals differ very greatly in their fat-carrying capacity. It is evident that the great majority of animals may be made to lay on fat by lessening their expenditure of energy or by increasing their intake of carbohydrates and fats. Since this is a perfectly physiological phenomenon, the only condition to explain is the excessive deposition of fat on a normal or reduced diet in the presence of a normal or even increased expenditure of energy. It has previously been pointed out that the metabolism of the fats may be dependent in some measure upon the secretion of some ductless gland. In the absence of this in-

¹ Jour. Biol. Chem., xiv, 1913, 117.

ternal agent, the oxidation power of the tissues is interfered with, thereby causing an excessive storage of this material. Secondly, obesity may be due to an unusually high efficiency of those organs which are directly concerned with fat metabolism, enabling them to keep the body as a whole in a proper condition on an unusually low supply of food. Obviously, this condition can only be remedied by a lessened ingestion of food and a greater expenditure of energy. The latter alone can do no good, because if the patient is then allowed to control his intake in accordance with his appetite, he no doubt would endeavor to balance the greater outgo by a greater intake. It should be remembered, however, that a fat person actually needs a slightly greater production of energy than a lean person, because his body surface is larger, favoring heat dissipation.

THE METABOLISM OF THE PROTEINS

The Source of the Protein of the Body.—It will be remembered that the proteins of the food are completely hydrolyzed into their amino-acids, and are absorbed as such and passed into the portal blood stream. Under ordinary conditions, the only slightly hydrolyzed products of protein digestion, such as peptone and proteose, are not absorbed in significant amounts, because it is a well-known fact that these substances, when injected directly into the blood stream, produce symptoms of intoxication. This anaphylaxis, however, does not follow if they are introduced into the intestinal canal. Whatever proportion of them may find its way into the epithelial lining cells must, therefore, be reduced and changed in its course through these cells into inert proteins. This change may also be effected while they circulate, because their concentration in the blood can never be increased sufficiently to produce injurious effects. Such a result is prevented ordinarily, because they are brought into contact with a very large quantity of blood, and because the quantity of the still unreduced protein within the intestine is very small. At all events, the evidence so far presented does not show that the intestinal lining cells synthesize the amino-acids into the proteins of the blood, which in turn would have to be changed into tissue proteins. Consequently, it may be concluded that the body synthesizes its proteins from the amino-acids directly, using in this case only those which are of special value to it. The others, as well as those transferred into the blood by the cells as waste, are split into two portions, one of which represents the ammonia and the other the remnant of the amino-acid molecule. The urea is derived from the former, while the latter is immediately oxidized to yield energy. For this reason, we commonly speak of the so-called *tissue-protein* and *circulating protein*, the former being represented by that portion of it which enters the cells of the tissues to become an intricate part of them, while the latter is broken down immediately without having been converted into cellular protoplasm.

The proportion of each must, of course, differ with the condition of the body. If the latter is in *nitrogen-equilibrium*, a more considerable proportion of it will be oxidized directly to yield energy than when the body is in need of this substance to make good a previous loss. Quite similarly, the greater the amount of protein taken in under normal conditions, the greater must be that amount of it which is directly converted into energy.

This division of the absorbed proteins into tissue and circulating proteins shows that their catabolism is not uniform, but consists essentially of two separate processes (Liebig). Obviously, the tissue catabolism must remain rather constant under normal conditions, while the catabolism of the circulating proteins must differ more directly with the amount of proteins ingested. Consequently, any attempt made to determine the metabolism of the proteins requires the reduction of the circulating proteins to a minimum. Only when this end has been accomplished are we in a position to obtain a fair insight into the protein metabolism of the tissues. Any analysis of this kind, therefore, must take into account first the so-called *exogenous protein*, namely, that portion of it which is derived directly from the food, and secondly, the *endogenous protein*, which is the result of the catabolism of the substance of the tissue cells. Clearly, the first has really little to do with the life of the cells, while the latter actually serves as a measure of the waste of the tissues.

The Utilization of the Proteins.—The amino-acids appear in the blood in amounts scarcely sufficient for a quantitative analysis. Van-Slyke,¹ however, states that their amount is fairly constant and that the fasting animal contains from 3 to 5 mgr. in each 100 c.c. of blood. After meals, when an active absorption of proteins is going on, their amount may be doubled and similar increases may be obtained by the injection of amino-acids into the intestine. Thus, 10 gm. of alanin administered in this way yielded as much as 6.3 mgr. in each 100 c.c. of mesenteric blood. A method by means of which such substances may be withdrawn from the circulating blood has been described by Abel.² It is known as *vividdiffusion*. The apparatus consists of a long tube of collodion coiled upon itself and immersed in a solution containing approximately the same content in salts as blood plasma. The ends of the collodion tube are connected with the central and distal ends of an artery. As the blood circulates through it, its diffusible constituents dialyze into the saline solution and may be recovered from the latter. In this way it has been possible to isolate alamine and valine in crystalline form, and also to detect the presence in the blood of histidine and creatine.

It is a well-known fact that a large meal of protein gives rise to a rapid increase of the urea in the urine until about the fifth hour, when at least 50 per cent. of the total nitrogen of the food will have passed into the urine. If we consider that digestion is going on mean-

¹ Harvey Lectures, New York, Lippincott and Co., 1916.

² The Mellon Lecture, Science, xlii, 1915, 135.

while, we must conclude that a portion of the nitrogen of the food passes over almost immediately. Consequently, urea may well be employed as an index of the amount of protein absorbed. Even the intravenous injection of solutions of the amino-acids into normal animals does not result in their retention, as much as 90 per cent. of the original amount disappearing from the blood in the course of 5 minutes after the injection. These facts, as well as others that might still be mentioned, show conclusively that the amino-acids do not tarry in the tissues, but are rapidly excreted so that their destruction practically equals their absorption. This need not surprise us, because it has been shown previously that the tissue proteins are equilibrated in a more exact manner than the fat and carbohydrates, and that a definite relationship must, therefore, be retained between the amino-acids of the blood and those of the tissues. But while the power of protein-storage of the tissues is extremely limited, it seems that the liver is much more elastic in this regard and is capable of assimilating 125 to 150 mgr. per 100 gr. of the original amount. Its power of absorbing this material is also evinced by the fact that the concentration of the amino-acids is less in the blood leaving this organ than in that entering it.¹

The deduction to be made from these data is that the liver utilizes the amino-acids in the formation of urea. But since this body may also be produced after the removal of the liver, this organ cannot be said to be the only place in which urea is formed, although it is safe to conclude that it is its chief source. Moreover, since it is the endeavor of the system to remain in nitrogen-equilibrium, it is the function of the liver to prevent any flooding of the tissues with amino-acids. Consequently, this organ begins its function of forming urea almost immediately after these substances have begun to be absorbed. Besides, the liver also takes care of the protein waste, discharged in consequence of the catabolism of the different tissues.

The End-products of Protein Metabolism.—Obviously, the tissue-proteins are first split up into the amino-acids from which they were first synthesized, and supposedly no decisive chemical difference exists between these catabolic products and the amino-acids absorbed. We know that the tissues possess this power of reducing their protein material, because they are in possession of proteolytic enzymes (proteases) which may be isolated from them in different ways. Thus, it is a matter of common experience that pieces of tissues, when kept under proper condition of temperature and moisture, undergo autolytic changes which yield ammonia, glycine, tyrosine, tryptolane and other basic substances. A similar process of autolysis occurs in malignant tumors, and such a condition as cystinuria merely indicates that the cystin is not taken care of by the body, owing to a derangement of the metabolism of the amino-acids. It enters the urine, frequently

¹ Mendel, *Ergebn. der Physiol.*, 1911.

associated with leucine and tyrosine, where it may be deposited in the form of calculi.

Whatever intermediary stages the amino-acids may pass through, they are finally converted into carbon dioxid, water, and relatively simple substances containing nitrogen. Chief among the latter is *urea* and its precursor *ammonia*, but there are also some which cannot be regarded as members of the amino-acid group, such as *creatine* and *creatinine*. These bodies are very largely the result of endogenous protein metabolism, although some of the creatine and creatinine of the food may appear as such in the urine. Besides, some of the amino-acids may appear in the urine as such, giving rise to the so-called *amino-nitrogen* or undetermined nitrogen. But since the metabolism of the cells also includes that of their nuclear material, and since the latter is also ingested, for example, in the form of sweet-breads or thymus, this list should be augmented to embrace the *purin bodies*. The determination of sulphur in the urine is valuable in so far as it gives a fair picture of the metabolism of the proteins, because this foodstuff serves practically as the only vehicle for its entrance into the body.

The purine bodies arise from purine. The first product of the oxidation of this body is hypoxanthine from which adenine is derived. The second product of its oxidation is xanthine and its amino derivative guanine. The trioxypurine is uric acid, which in birds and reptiles is the chief derivative of protein metabolism. Whether this substance is also excreted by the mammals in important amounts is still a question.¹ It would appear, however, that the urine acquires uric acid and also a certain amount of purine bases after a copious diet of meat and especially after the ingestion of glandular material. For this reason, Burian and Schur² have recognized an endogenous and exogenous purine metabolism, the former having to do with the reduction of the purine of the tissues and the latter with that of the preformed purine constituents of the food ingested. In general, it may be said that the exogenous purine bears a close relation to the purine of the urine. If it accumulates in the tissues it gives rise to the condition known as gout, and hence, purine-rich food should not be taken by persons who suffer from this metabolic difficulty or tendency (gouty diathesis). More recently, it has also been shown by Ascoli and Izar³ that purine may be synthetized in the mammalian body from urea and carbon-rich residues, two molecules of the former uniting with a carbon residue containing three carbon atoms. This purine would of course be endogenous in its character.

¹ Jones, Nucleic Acid, Monographs in Biochem., Longmans, Green and Co., 1914.

² Zeitschr. physiol. Chemie, xxiii, 1897, 55.

³ Ibid., xliii, 1911, 319.

CHAPTER LXXXVII

THE METABOLIC REQUIREMENTS OF THE BODY

The Effect of Starvation.—The withholding of food places the animal upon its own resources. The tendency must then be to conserve its most important metabolic substances, the proteins, and to obtain its energy from the carbohydrates and fats. We observe, therefore, that the tissues of an animal really fall into two groups, namely, those which form the metabolic nucleus of the body and those which serve principally as storehouses for energy-yielding material. A starving animal first of all draws upon its store in glycogen, then upon its fat, and lastly, as an emergency measure, upon its proteins.

Obviously, energy must be produced even in the advanced stages of inanition, but naturally, its amount must then be slight, because all the activities of the body are greatly reduced during this period. This in itself will tend to conserve the resources of the tissues. Thus, inanition gives rise almost immediately to a feeling of fatigue and weakness which the animal complies with by assuming an inactive position, passing its days in sleep and semi-stupor. The rate of respiration, the frequency of the heart, as well as the body-temperature, are those of a resting animal and remain so until a day or two before death, when the respiratory and cardiac activities are greatly reduced and the body-temperature falls very markedly. The quantity of the urine is greatly decreased, and so is its content in urea. Feces are formed until about the time of death, but in very small amounts, say, 10 to 20 grm. in the course of a day. Professional fasters, however, state that no pain is experienced at any time during the fast and that the uncomfortable sensations of the first few days disappear very quickly. The body-weight decreases steadily, until at the end of 10 days this loss may amount to about 1.0 or 1.5 per cent. of the original weight. Naturally, those tissues are reduced most which contain the largest amount of fat, whereas the brain, spinal cord, heart, lungs, and pancreas suffer least.

This discussion shows first of all that an animal which is in possession of a considerable amount of fat at the beginning of the period of starvation, is in a much better position to withstand the withdrawal of food than one not protected in this way. Thus, a well-nourished dog may survive a period of starvation lasting 4 weeks; in fact, in some instances death did not result until after 2 or 3 months.¹ Succi, the professional faster, abstained from food for 30 days, and Marlatti for 50 days.² The small mammals die much sooner, and

¹ Falck, Beitr. zur Physiol., Marburg, 1875, and Kumagawa, Archiv für Physiol., 1898.

² Luciani, Das Hungern, 1890.

reptiles and amphibia not until after many months and possibly a year. Secondly, it may readily be gathered that the production of heat in starving animals must be greatly reduced. Thus, the professional faster Cetti¹ required on the first day only 32.4 calories for each kilogram of his body-weight and, on the fifth day, only 30.0 calories. Similar values have been found by Tigerstedt.² In accordance with Rubner³ and Magnus-Levy,⁴ this loss of energy is only 7 to 15 per cent. lower than that in a person ingesting a moderate amount of food.

The course of the *elimination of nitrogen* during periods of starvation is closely dependent upon the condition of the animal at the time of withholding the food. If the animal has been accustomed to ingest large amounts of protein material, its protein-catabolism will be rather high during the first few days of the period of starvation, but a uniformly low output of nitrogen will have been reached at the end of about a week. Meanwhile, its store in glycogen will have become exhausted, while its fats will have been drawn upon incessantly to shield its proteins. As soon as all the available fat has become exhausted, a more intense metabolism of the proteins sets in, in consequence of which the output of nitrogen is increased. This *'premortal rise in the excretion of nitrogen'* constitutes an unfavorable diagnostic sign, because it indicates that the ordinary fuel of the animal has been thoroughly depleted.

In the herbivora, conditions are somewhat different, because these animals possess a large store of glycogen. Thus, it is commonly found that their output of nitrogen is considerably increased during the first days of the period of starvation, because since they have been accustomed to use carbohydrates as their chief fuel, the sudden withdrawal of this foodstuff forces them to fall back upon their store of proteins. A very similar reaction takes place in men who have been accustomed to eat large amounts of carbohydrates. In both instances, therefore, starvation changes the metabolism into a type more nearly like that of the carnivorous animals.

The *ingo of oxygen and outgo of carbon dioxid* soon reach a minimal value. *Urea nitrogen* falls and NH_3N rises, but the total amount of creatinine and creatine, which form peculiar derivatives of the metabolism of muscle tissue, is not changed materially. The excretion of the *purines* is decreased at first and then increased, owing, in all probability, to the steady destruction of the nuclear material. As far as the relation of the *sulphur* to the nitrogen is concerned, it is to be noted that their ratio is at first as 17N:1S, and later on, as 14.5N:1S. If anything, these values suggest that the principal source of protein during the later stages of starvation is the protein material of muscle tissue.

¹ Virchow's Archiv, cxxxi, 1893; also: Benedict, Carnegie Inst. of Washington, No. 126, 1910.

² Skand. Archiv für Physiol., vii, 1897, 29.

³ Gesetze des Energieverbr., Leipzig, 1902.

⁴ Pfüger's Archiv, lv, 1894, 96.

The Effect of Sleep.—Sleep does not affect the metabolism of the proteins to any extent, as is shown by the fact that the total nitrogen excreted remains about the same. Instead, there appears a slight reduction in the output of endogenous purine nitrogen, indicating a lessened destruction of nuclear substances. Contrariwise, the ingo of oxygen and outgo of carbon dioxide are markedly diminished, an indication that the tonicity and activity of the muscles and glands are considerably reduced.

The Effect of Temperature.—Within narrow limits the metabolism of the warm-blooded animals is increased by a cold and decreased by a warm outside temperature, but this result is only obtained if the body-temperature is not greatly altered thereby. Extreme variations in the outside temperature, which in turn produce a material change in the body-temperature, affect the metabolism in a reverse manner. This need not surprise us, because the body constantly attempts to retain its normal temperature of about 37.0°C . A cooling of the air gives rise to a greater loss of heat and hence, a more intense metabolism must immediately be instituted to counteract this effect. Contrariwise, an increased temperature of the atmosphere lessens the loss of heat and, consequently, less heat need be produced. But, in case this heat-regulatory mechanism is overcome, an excessive fall in the body-temperature invariably diminishes the oxidations and heat production, whereas an unusual rise increases these processes. The body having been sufficiently cooled, all chemical processes within it come to a standstill. Evidently, in the presence of a well-balanced heat-regulatory mechanism, any deficiency in the body-temperature is made up at the expense of the non-nitrogenous constituents of the tissues. This is shown by the fact that the consumption of oxygen and elimination of carbon dioxide are increased, while the nitrogenous excretions in the urine remain practically the same.

The Effect of Age and Sex.—The output of energy is low in the new-born, but increases rapidly during the first year until it reaches its maximal value at about the sixth year. Subsequent to this time, it decreases rather rapidly until the twentieth year and then more slowly until late in life. This steady decline is interrupted only at the time of puberty, when the metabolism is temporarily intensified. The output of energy by the female is about 4.3 per cent. below that of the male.

The Effect of Muscular Exercise.—The metabolism is materially increased even by ordinary degrees of work, although the protein waste is no greater than during rest. After excessive exercise, on the other hand, the latter is considerably increased, embracing urea, ammonia, creatinine, and even uric acid and purine bases. This contradicts the view of Liebig, implying that the greater energy liberated during muscular work finds its source in a break-down of the muscular tissue, and must, therefore, be performed at the expense of an increased metabolism of the proteins. Such a result, however, is never obtained

unless the animal has been nourished exclusively on protein material and is not in possession of normal amounts of glycogen and fat. Thus, Voit has found that an animal which is in fat and carbohydrate equilibrium does not exhibit a nitrogenous breakdown, and concluded, therefore, that the extra energy is derived wholly from the non-nitrogenous constituents of the body.

These results soon found support in the experiments of Fick and Wislecinius, who ascended the Faulhorn to a height of 1956 meters. By comparing their weight with the height to which they climbed, it was possible to compute the amount of work performed by each of them. In the case of Fick, it amounted to $66 \times 1956 = 129,096$ kilogrammeters plus about 30,000 kilogrammeters of work performed by the heart and muscles of respiration. Since only non-nitrogenous food had been ingested by these investigators during a period of 17 hours before the climb as well as during it, the urea eliminated by them must have been derived entirely from their body-proteins. On determining the heat value of this urea, it was found to be entirely insufficient to account for the amount of work done. Very similar results have been obtained by Parkes upon soldiers during periods of rest and long marches, and by Atwater by means of the respiration calorimeter.

It may be concluded, therefore, that ordinary muscular work does not increase the metabolism of the proteins much beyond its normal value, provided sufficient non-nitrogenous material is at hand to produce the required amount of extra energy. Accordingly, if the non-nitrogenous substances are present in insufficient quantity, some of this extra energy must be derived from the proteins. The elimination of nitrogen in the urine is then increased, and naturally, this waste must be the greater the more intense the muscular exercise.

Normal Metabolism.—The preceding discussion pertaining to starvation is of special value, because it furnishes a means of determining the amounts of energy liberated by the body under normal conditions, and allows us to ascertain the amount of fuel which must be ingested in order to supply this energy. It will be found that a marked difference exists between the various foodstuffs in this regard. In the first place, it should be noted that an animal fed on pure fat or carbohydrate, or a mixture of the two, does not survive this diet for a much longer period than if all food were withheld. Consequently, this diet is only little better than actual starvation. On a diet of proteins, salts and water, on the other hand, the animal most generally survives. In the second place, it is not correct to assume that an animal may be kept in equilibrium for any particular foodstuff if the intake is exactly balanced with the waste.

This is true in particular of the proteins. Thus, if a starving animal is fed an amount of protein which exactly balances the output of nitrogen, the excretion of the latter rises to a level practically equal to that of starvation, plus that of the protein ingested. This implies

that the waste of tissue-proteins proceeds as before. To illustrate, if a dog of medium size excretes on the fifth day of starvation about 5 gm. of nitrogen, this loss corresponds to a combustion of 31.25 gm. of protein. Now, if the latter amount be given to this animal as food, it will excrete nearly 10 gm. of nitrogen-waste. In order to cause this animal not to lose more nitrogen than it receives, or better, in order to place it in nitrogen-equilibrium, it is necessary to give it an amount of protein the nitrogen-content of which is at least two and one-half times that of the starvation standard. This same conclusion may be arrived at by a consideration of the data derived from professional fasters. Since the total output of energy, say, on the fifth day of the period of starvation, amounts to 1979 calories and the output of nitrogen to 11.44 gm., it requires 71.5 gm. of protein to meet this loss. But 71.5 gm. of protein yield only 293 calories and hence, the aforesaid amount of energy cannot be derived entirely from this protein. The balance must be supplied by the tissue-fat and glycogen. Consequently, the loss in the substance of the body cannot be stopped by balancing the output of nitrogen by an equal ingestion of proteins. While it is quite simple to retain by this means the nitrogen-equilibrium in the strictly carnivorous animals, it cannot be kept in this way by the herbivora and omnivora.

Since man belongs to the latter class and requires about 3000 calories for his daily work, it will be seen that at least 3 lbs. of lean meat must be ingested by him in order to supply this amount of heat, 1 lb. of meat yielding less than 1000 calories. But this method of furnishing the necessary energy for the body soon overtakes the organs of metabolism and places the person in the condition of partial starvation. These facts form the basis of Banting's cure¹ for obesity which, by the ingestion of lean meat, attempts to give the feeling of satisfaction connected with a "square" meal, and at the same time causes the body to burn up its reserve materials, retaining as far as possible its proteins.

If the starving animal is fed a mixed diet instead of pure protein, it is able to retain its nitrogen-equilibrium with much less difficulty, because the ingestion of the proteins can then be made to approximate the waste. The carbohydrates and fats are protein spacers. This is true especially of the carbohydrates, because it has been shown that the combustion of proteins during starvation may be greatly reduced by the ingestion of this foodstuff. Thus, the administration of a large meal of carbohydrates to a starving animal may raise its respiratory exchange 20 to 30 per cent. Furthermore, it is possible by this means to reduce the daily output of nitrogen in men who partake of an average diet of from 15 gm. to 6 gm. and less, without causing them to lose their nitrogen-equilibrium. The amount of carbohydrate ingested must, of course, balance the normal daily expenditure of energy. This subject may also be approached the other way, *i.e.*, by determining the amount

¹ Advocated by Wm. Banting, an undertaker of London, 1797-1878.

of protein which must be ingested in order to bring a person into nitrogen-equilibrium. To attain this end we need 30 grm. of the proteins of meat, 31 grm. of the proteins of milk, 54 grm. of the proteins of beans, 76 grm. of the proteins of bread, and 102 grm. of the proteins of corn. This outline shows very clearly that the proteins of the vegetables are not so easily assimilated as those of meat.

Excessive Metabolism.—The body safeguards itself against possible disorders in its metabolism first by the quality and secondly, by the quantity of the food. It constantly endeavors to retain a normal balance sheet. Under ordinary conditions, however, more material is ingested than is actually required to preserve its metabolic equilibrium. This fact has led some physiologists to believe that a certain *luxus consumption* is a necessity in order to allow for a definite waste. Any excessive ingestion, on the other hand, leads as a rule to a certain deposition of the superfluous material in the tissues. Thus, if a normal animal is given excessive amounts of fats and carbohydrates, a large portion of these foodstuffs is converted into glycogen and tissue-fat without materially increasing the general metabolism. In the case of hyper amounts of proteins, however, no significant storage takes place, and by far the largest part of this substance is excreted directly. Consequently, the output of nitrogen may be employed as an index of the amount of proteins ingested.

This fact shows very clearly that a *luxus consumption* in the case of proteins cannot serve an important purpose, and is very expensive besides. Chittenden has proved that a normal nutritive condition may be attained on a mixed diet containing only 7 grm. of nitrogen daily. Men partaking of this diet followed their ordinary vocations without difficulty, and yielded from 32 to 35 calories per kilo of their body-weight. In fact, when somewhat larger quantities of carbohydrates and fats were given, the nitrogen ingo could be reduced to 5 grm. daily (33 grm. of protein). While these experiments indicate that a normal person can get along with less protein than he usually takes, the question as yet to be decided is: should he actually so deprive himself for his own benefit? Quite aside from an actual *luxus consumption*, the answer might be that a material reduction in the ingo of protein material would undoubtedly lower the resistance of these persons, at least in the course of time. Much also depends upon the quality of the protein. The accepted view, however, is that a reduction in the intake of proteins of one-third to one-half might be effected without injury and, naturally, this necessary minimum of about 50 to 60 grm. of proteins, instead of the usual 100 to 150 grm., must be supplied in the form of meat and vegetables to the exclusion of neither. As has been stated above, much larger amounts of the latter must be ingested in order to furnish the same amount of energy.

The foregoing discussion must have shown that an animal may be in nitrogen-equilibrium and not in carbon-equilibrium. The latter, however, is not so important, because the quantity of fat may vary

considerably, while the nitrogen content remains practically the same. Obviously, a gain in carbon means a gain in fat, and *vice versa*. In the carnivorous animals, the carbon-equilibrium is retained on an abundant protein diet, but this foodstuff must be supplied in excessive amounts. Thus, Voit has shown that the larger carnivora need at least 1500 gm. of meat daily to prevent a loss of carbon. For a man weighing 70 kilos, this would mean an ingestion of 2000 gm. of lean meat, and a combustion and elimination of nitrogen about three times greater than normal. Obviously, a metabolism of this kind could not be continued for any length of time. This again shows the necessity of a mixed diet, as being more beneficial and economical.

CHAPTER LXXXVIII

THE NUTRITIVE VALUE OF FOOD

The Normal Diet of Man.—The quantity of food which is required to keep a person in a condition of health is determined by its power of sustaining the energy which he is called upon to liberate. While the latter must vary considerably with the activities of the body, we may adhere rather closely to the data of Rubner which show the following energy requirements:

Weight, kilos	Area, sq. m.	Calories	Calories per kg.
80	2283	2864	35.8
70	2088	2631	37.7
60	1885	2368	39.5
50	1670	2102	42.0
40	1438	1810	45.2

Thus, it will be seen that a vigorous man weighing 70 kilos necessitates close to 37 calories for each kilogram of weight, or about 2600 calories in all. During starvation this same person needs 32 calories per kilogram, or 2200 calories in all. Consequently, the ordinary requirement is about 14 per cent. above that of starvation. In order to supply this energy, Voit gives the following ration for the use of workmen performing 8 to 9 hours of work: proteins 118 gm., fat 50 gm., and carbohydrate 500 gm. This would yield 3055 calories which, owing to a certain non-utilization, may be reduced to about 2700 calories. Rubner allows 127 gm. of protein and Atwater¹ 125 gm. for this class of workmen. Furthermore, in the case of severe work

¹ Physiologie des Stoffwechsels, 1881.

² Mem. of the Nat. Acad. of Sciences, Washington, 1902.

this supply must be increased considerably, thus: proteins 135 gm., fat 80 gm., and carbohydrate 500 gm. This represents a total value of 3348 calories.

It will be observed that the amount of protein remains fairly constant, while the proportion of carbohydrate and fat varies considerably. Moreover, these nutritive substances may be substituted for one another within narrow limits, but none of them should be eliminated from the diet altogether, because the retention of perfect health requires the ingestion of a certain minimum amount of each. Various other factors must also be considered. For example, if there has been a loss of protein material from one cause or another, it is imperative to ingest an extra amount of protein to allow for its storage in the form of tissue proteins. Quite similarly, it is desirable to increase the protein metabolism during periods of training, when a perfect stability of the musculature is to be attained. A limited reduction in the amount of the protein is justifiable only in vigorous persons.

Whether the prerequisite amount of protein is derived from animal food or from vegetables is rather immaterial, although much quicker results are obtained with the former. Both have their advantages and disadvantages. While vegetables are efficient protein producers, much larger quantities of them must be ingested in order to yield the same degree of energy. In the end, this may not prove to be an economical advantage, at least not at the present time. They possess, however, certain stimulating qualities upon peristalsis and bring into the body a greater variety of proteins than could possibly be introduced by meat alone. It appears, therefore, that the ordinary person should partake of a mixed diet rather than of one strictly vegetarian in its character.

It has been observed by Rubner that a starving animal, when fed with carbohydrate, shows an increase in its heat production of from 30 to 40 per cent. The feeding of meat also gives rise to an increase under this condition, but the increase is then almost three times greater. It will be seen, therefore, that the proteins are actual stimulants of metabolism and possess for this reason a *specific dynamic action* upon the organs of metabolism.

The Factor of Growth.—In accordance with the well-established fact that the intensity of the metabolism increases inversely with the size of the animal, it cannot surprise us to find that children must compensate for a much greater expenditure of energy than adults. Small animals invariably lose more heat in proportion to the mass of their body than large ones, although area for area of their body-surface their dissipation of heat is practically the same. In order to make up for this greater loss of heat, children must be more active. This is true especially of boys before the age of puberty. In addition, it is not at all improbable that a second factor is at work at this time in the form of some stimulus derived from energized and growing protoplasm. Thus, a body between the ages of nine and fourteen requires as much

food as an adult, and between the ages of fourteen to nineteen even more than that. In the females there is a similar absolute increase to about the eleventh year, when it becomes more constant and equals about that of a woman of thirty. These brief data show very clearly that the total energy and food requirements of the young animal are higher than those of the adult. In the second place, it has been made evident by the work of Mendel¹ and others that growing tissues demand not only an abundance of protein, but proteins of the proper kind.

This statement leads us to infer that a diet may be well balanced, as far as the ingo and outgo of the proteins are concerned, and yet fail absolutely in supplying those substances which are absolutely essential to growth. Thus, it has been shown by Osborne, McCollum and others that such proteins as legumelin (soy bean), gliadin (wheat and rye), legumin (pea), hordein (barley), zein (maize), and phaseolin (kidney bean) may maintain life, but prove quite insufficient for growth. Other proteins which are capable of sustaining growth are glycinin (soy bean), gluten (wheat), glutelin (maize), globulin (squash seed), edestin (hemp seed), and casein. In the case of casein it is of interest to note that it does not contain glycocoll, one of the simplest of the amino-acids, but this deficiency does not prove disturbing, because the body is in a position to synthesize this substance from other sources. Just the opposite result follows the withdrawal of cystine, which the body cannot build up and must, therefore, obtain in an available form. Quite similarly, the tissues may be maintained in their present condition without lysine, although they cannot grow in its absence. This substance seems to be a requirement of all growing tissues, because it is present in large amounts in casein, lactalbumin and egg vitellin. It will be seen, therefore, that the body demands a mixture of protein foodstuffs from which it may then select those amino-acids which are most essential for its growth. An exclusive vegetable diet might easily prove insufficient, because it lacks the aromatic amino-acids, tyrosine and tryptophane, the diamino-acid, lysine, and the sulphur amino-acid, cystine. But this is also true of certain proteins of animal origin; for example, gelatin, which for this reason cannot be regarded as an adequate food.

Since milk is practically the sole food of the growing mammal, we should expect to find its content in proteins to correspond closely to the above principles. In support of this contention it might be mentioned that the analyses of milk from different animals have shown that the protein content of this secretion varies with the speed with which their young grow. For example, since the infant doubles its weight in about 180 days and the kitten in 7 days, human milk contains only 1.6 per cent. of protein and that of the cat 9.5 per cent. Furthermore, the infant receives a relatively much greater proportion of protein than the adult and, besides, an excess of fat in order to be

¹ Harvey Lectures, Lippincott and Co., New York, 1915.

able to utilize the former as tissue-protein and to burn the latter to produce heat. In view of the larger body-surface of the infant and its more intense metabolism, such a relationship is rather to be expected. Milk is also rich in calcium and phosphorus, a peculiarity which greatly favors the growth of the skeleton.

The Inorganic Salts.—So far special attention has been paid to the carbohydrates, fats and proteins. It is to be noted, however, that an animal which receives these foodstuffs without the salts, succumbs even more rapidly than one fed with an absolutely inadequate diet. Evidently, the inorganic constituents are as important for the maintenance of life as the organic constituents, and this in spite of the fact that they do not yield energy. They are absolutely essential to the body for the reason that they help in maintaining the composition and osmotic pressure of the body-fluids and determine, therefore, the interchanges of its metabolites. Secondly, they form essential constituents of the frame-work of the body and even enter into the composition of its soft parts. Thus, it will be found that the incineration of the body yields about 4.3 to 4.4 per cent. of its weight in ash. Of this amount, five-sixths must be apportioned to the bones and one-sixth to the soft parts. The ash consists of the chlorids, phosphates, sulphates, carbonates, fluorides and silicates of potassium, sodium, calcium, magnesium and iron. Besides, iodine occurs in the tissue of the thyroid gland. It is also evident that the potassium salts belong more particularly to the organized elements of the tissues, whereas the sodium salts are more directly concerned with the composition of the body-fluids, and the calcium salts with that of the bones.

In the latter case, it has been demonstrated beyond doubt that a diet poor in calcium gives rise to rickets, a condition characterized by a deficient and imperfect growth of the bones. In adult life, most of the calcium ingested is again excreted in the feces and urine, although an excessive storage may result later on which leads to a brittle condition of the bones and calcareous infiltrations of different tissues, such as the walls of the blood-vessels. Iron enters the body in organic combination, and it is still a much debated question whether inorganic iron can actually be taken up and converted into so complex a substance as hemoglobin.

Bunge¹ has called attention to the fact that man and the carnivorous animals have no especial longing for salts, whereas the herbivora and vegetarians seek it eagerly. With the exception of sodium chlorid, however, these salts are taken into our system unconsciously in combination with the different foodstuffs, but the addition of considerable amounts of the former to our food does not seem to be a necessity, inasmuch as 1 to 2 grm. of it suffice for ordinary purposes. Consequently, the daily ingestion by the average man of 10 grm. of this salt may rightly be considered to be far in excess of his actual needs. Bunge explains this large intake of sodium chlorid by saying

¹ *Physiol. des Menschen*, 1901.

that the potassium sulphate, which is so abundant in vegetables interacts with the sodium chlorid of the blood, forming potassium chlorid and sodium sulphate. Both salts are then removed in the urine and hence, it becomes imperative to renew the sodium chlorid content of the blood repeatedly in order to keep it fairly constant.

Accessory Factors.—Besides the digestibility and nutritive value of the diet, practical dietetics must also pay attention to its palatability. This involves *cooking* and the addition to the food of flavors, condiments and stimulants. The first factor is important first of all from an economic standpoint, because it tends to render the cheaper foods more available and to decrease the perfectly appalling waste of all food. Secondly, it makes the food more appetizing and destroys its indigestible envelopes so that the digestive juices are able to attack the nutritive material directly. Thirdly, it destroys parasites and microorganisms and those antibodies which might inhibit the action of the digestive juices. Thus, it is a well-known fact that raw white of egg is not digested in the stomach, because it contains an antibody which hinders the action of the pepsin, while a finely divided boiled egg is more rapidly acted upon by this enzyme. Lastly, cooking is of importance because it renders the food more bulky and macerates the cellulose material of green food so that it can be more advantageously utilized as ballast for the feces. This in itself stimulates peristalsis and liberates certain substances possessing a laxative action.

The *flavors and condiments* have no especial food-value, but are of importance because they make the food more appetizing. They are divided into (a) aromatics, inclusive of such substances as cinnamon, vanilla and nutmeg, (b) pepper, (c) alliaceous substances, such as garlic and mustard, (d) acid condiments, such as pickles, vinegar and citron, (e) salty substances, such as the ordinary table salt, and (f) sugar.

The *stimulants* consist of wine, beer, tea, coffee, chocolate and cocoa. While some of these contain considerable amounts of nutritive material, their principal action is very similar to that of the condiments, *i.e.*, they render the food appetizing and stimulate the secretions. However nourishing a food may be, it eventually produces an antagonistic effect unless mixed with these stimulants. Thus, the rind of the bread, the skin of fruits, and extracts of meat are almost as important as the foodstuffs contained in these articles of diet. Besides, such articles as beer and cocoa possess a distinct nutritive value, although they do not form an adequate food when ingested alone. Thus, 14 liters of beer would be required to yield 15 gm. of nitrogen, and 10 liters of it to furnish 250 gm. of carbon. In the case of cocoa, we obtain as much as 50 per cent. of fat, 4 per cent. of starch and 13 per cent. of proteins, but excessive quantities would have to be consumed in order to satisfy our caloric needs. Its stimulating alkaloid is theobromine or dimethyl xanthin ($C_7H_8N_4O_2$), which exerts a tonic action upon the nervous and vascular system similar to that of caffeine.

The usual stimulant taken by healthy persons is coffee or tea. In addition to ethereal oil, tannic acid and other substances, these articles contain the alkaloid caffeine (Runge, 1820) or theine. Coffee differs from tea in being rich in aromatic material (caffeal). Tea contains a bitter substance, tannin, and hence, it should not be allowed to draw for longer than a few minutes, otherwise too much tannin will enter the solution and produce injurious effects. Similar stimulating drinks are the mate of Paraguay, the guarana of Brazil, the bush-tea of South Africa, and the cola of Central Africa. Not being in possession of caffeine plants, the inhabitants of Mexico derive their stimulating beverage from the fermented seeds of the chocolate plant which contain theobromine.

Among the alcoholic stimulants might be mentioned the malt liquors, red and white wines, fortified wines, distilled liquors, or spirits, and elixirs. Having a great affinity for water and being a coagulant of protein, alcohol tends to destroy the cells. It should, therefore, be regarded essentially as a protoplasmic poison. Regarding its action as a stimulant and its value as a food, the reader must be referred to the more specialized literature upon this subject, because it is altogether too contradictory and extensive to be included in a book of this kind.¹ In general, however, it may be said that alcohol does not build up the tissues, although it may serve to spare and to replace fats and carbohydrates for a time and also to protect the proteins. For this reason, it may be considered as an adjunct article of diet but not as a true food. Obviously, its properties of yielding energy are completely overshadowed by its pharmacologic actions as a depressant and irritant.

¹ Welch, "The Pathological Effects of Alcohol;" Abel, "The Pharmac. Action of Alcohol," and Atwater, "The Nutritive Value of Alcohol," in *Physiol. Aspects of the Liquor Problem*, 1903.

SECTION XXVIII

EXCRETION

CHAPTER LXXXIX

THE SECRETION OF URINE

General Discussion.—The term excretion is commonly applied to that process which purposes to remove the waste products from the body. Living matter undergoes constant metabolic changes, and it is essential that the substances formed in the course of these processes be removed as quickly and thoroughly as possible. But this statement does not imply that the substances previously taken into the body, are simply split into their components and excreted, because in several instances the end-products are first converted into by-products by synthesis. In other words, excretion should not be thought of as a passive elimination of the simple constituents of the food, but rather as an active cellular synthesis. It is also evident that this process must concern itself with the elimination not only of fluids, but also of semi-solid material as well as of gases, and this is true of each individual cell as well as of the body as a whole. Thus, cellular dissimilation counterbalances cellular assimilation, whereas excretion counterbalances the nutritive material ingested.

On the excretory side of metabolism matters are relatively simple, because, while gases and liquids of varying composition are involved, the number of the excretory channels may really be reduced to four, namely, the skin, lungs, alimentary canal and kidneys. The chief gaseous excretion is furnished by the lungs in the form of carbon dioxid. It constitutes the final stage in the elimination of the carbon of the absorbed food. The principal fluid excretion is furnished by the kidneys in the form of the urine, which contains the hydrogen and unchanged water of the food as well as the various end-products of protein metabolism. But the hydrogen and unchanged water of the food are also eliminated by the skin, lungs, intestinal canal and, in a small measure, also by the nasal mucosa, lacrimal glands and mucous glands. The undigested and unabsorbed portions of the food, as well as certain true excretory materials, are eliminated in the feces.

The Structure of the Kidney.—The urinary organs embrace the two kidneys, the two ureters, and the urinary bladder with the urethra. In man each kidney is invested by a fibrous capsule and is deeply imbedded in the fatty tissue of the lumbar region. Its capsule is only

slightly adherent to its substance and is continued onward as the external coat of the upper and dilated segment of the ureter. In transverse section each kidney presents two rather sharply differentiated portions, namely, an outer or cortical and an inner or medullary. This difference in the appearance of its cut surface is due to the peculiar distribution of the urinary tubules, of which practically its entire substance is composed. Consequently, it may be said that the kidney is a compound tubular gland, the individual secretory units of which are directed radially outward from a common central reservoir, known as the pelvis. For this reason, the beginning portion, or glomerulus, of each urinary tubule must come to lie much closer to

FIG. 522.

FIG. 522.—DIAGRAMMATIC VIEW OF THE KIDNEY IN LONGITUDINAL SECTION, SHOWING THE ARRANGEMENT OF THE URINIFEROUS TUBULES.

G, Glomerulus; *P*, pelvis; *V*, ureter; *C*, cortical substance; *M*, medullary substance.

FIG. 523.

FIG. 523.—GLOMERULUS WITH THE BEGINNING SEGMENT OF THE URINIFEROUS TUBULE.

G, Glomerulus; *A* and *E*, afferent and efferent blood-vessels; *C*, capsule of Bowman; *N*, neck of uriniferous tubule; *CT*, distal convoluted tubule.

the surface of the organ than its collecting segment. The renal cortex, therefore, is made up principally of the glomeruli and distalmost portions of the uriniferous tubules, while the medulla contains chiefly the smaller and larger collecting channels as they strive to attain the cavity of the pelvis.

Each tubule begins as a dilatation in which is suspended a coil of capillaries. The former constitutes the capsule of Bowman and the latter the corpuscle of Malpighi. At its point of exit from this enlargement the tubule is highly constricted, forming here the so-called neck of the tubule. It then pursues a serpentine course, its entire segment of it being known as the first or distal convoluted tubule. Then follows a narrow, straight portion which actually enters the medulla but soon recurs as a straight segment parallel to the former. These constitute the descending and ascending limbs of the U-shaped loop of Henle. Having reentered the cortex, the tubule again pursues a wavy course and forms the second or proximal convoluted tubule. It now unites with others of the same kind into smaller collecting channels

and these in turn into larger ones until about a dozen conical bundles have been formed, each of which constitutes what is known as a pyramid. The pointed extremity or apex of each pyramid projects well into the pelvic cavity, subdividing the latter into a number of recesses. The pelvis is in free communication with the ureter of which it really forms its funnel-shaped upper expanse.

FIG. 524.—DIAGRAMMATIC REPRESENTATION OF THE BLOOD-SUPPLY AND COURSE OF THE URINIFEROUS TUBULE.

J, Interlobular blood-vessels derived from arches between cortex and medulla; *G*, glomeruli; *C*, distal convoluted tubule; *D* and *A*, descending and ascending limbs of the loop of Henle; *CT*, collecting tubule; *P*, papilla and pelvis of the kidney.

which they form a rather close network. This plexus is known as the renal plexus. It contains afferent and efferent fibers which are chiefly concerned with the activity of the blood-vessels, although it has been claimed that they are also secretomotor in their function. Preganglionically these fibers are contained in the greater and lesser splanchnic nerves.

The flattened epithelium of Bowman's capsule is reflected over the tuft of capillaries. In the distal convoluted tube, however, the lining consists of high and markedly granular cells which exhibit a peculiar brush-like outer margin and vesicular formations. In the descending limb of the loop of Henle, the cells are flat and clear, while those of the ascending limb are again higher and striated. These changes in the character of this epithelium are responsible for the relative narrowness of the lumen of the ascending limb. The cells of the proximal convoluted tubule again present a decided fibrillated appearance. Those of the collecting channels are cuboidal or columnar in shape and quite clear.

The arterial supply of the kidney is derived from the renal artery. Its two terminal branches break up into smaller ones which pass at first directly outward but bend at almost right angles as soon as they have reached the junction between the medulla and cortex. From these arched transverse vessels arise the interlobular arteries which are directed straight toward the surface of the organ and give off here and there transverse branches which finally form the tufts of capillaries, previously described as the Malpighian corpuscles. Each glomerulus, therefore, consists of an afferent vessel representing one of these branches, and a much narrower efferent vessel which, after leaving this structure, ramifies extensively between the different convoluted tubules.

This capillary network then gives rise to the interlobular veins and these in turn to the renal vein. The medulla derives its blood-supply from straight arterioles which arise from the transverse arterial arches. These constitute the arterial rectæ.

The nerves innervating the kidney are derived from the suprarenal plexus and follow the highway of the artery around

Theories of Urinary Secretion.—The kidney is the most important excretory organ of the body. Its function is to separate the constituents of the urine from the blood—its watery part as well as its solids. Upon it, in particular, rests the maintenance of the composition of the body-fluids; and hence, it must keep up an almost continuous activity which cannot be compensated for by any other organ. Thus, it is a well-known fact that the removal of both kidneys is fatal, owing to the accumulation in the blood of the end-products of protein metabolism. The same result follows the ligation of both renal arteries, but the extirpation of only one organ usually produces no untoward effects, because the opposite organ then enlarges and accomplishes the work previously performed by the two organs together.

The modern views regarding the manner in which the renal tubules perform their work, is based upon the older theories of Ludwig¹ and Heidenhain.² The former embodies the simple physical principles of filtration and diffusion and the latter, these principles in conjunction with a secretory activity on the part of the lining cells of the tubules. The filtration theory of Ludwig holds that the glomerulus plays the part of a filter, giving rise to a quantitatively and qualitatively complete urine under the pressure of the blood. This structure, therefore, constitutes the most important segment of the urinary tubule, while the others fulfill merely the function of a conducting channel. In substantiating this view, Ludwig laid particular stress upon the structural peculiarities of the glomerulus, emphasizing the fact that it consists of a coil of capillaries which are suspended in a double-walled capsule. Moreover, the narrowness of the efferent vessel tends to augment the lateral pressure and to diminish the velocity of the blood-flow. As far as the pressures are concerned, it will be noted that a capillary blood pressure of 40 to 60 mm. Hg. is in this instance contrasted against a pressure of about zero, thus affording most favorable conditions for a passive transfer of the constituents of the blood into the capsule of Bowman. In the tubule this process is then augmented by an endosmosis between the concentrated blood and the watery urine which leads to a passage of the molecules of water from the urine into the blood until the former has acquired its normal consistency. This process of reabsorption of water from the urine Ludwig conceived as purely physical diffusion, although he clearly recognized the fact that this process may undergo decided changes in consequence of the administration of diuretics, such as urea and sodium chlorid.

In 1842 Bowman³ expressed the idea that the glomerulus serves merely as the seat of the secretion of the watery part of the urine, whereas its solid constituents are formed in the tubule itself. In analogy with his work upon other glands, Heidenhain then promulgated the theory that the urine is not produced solely by filtration and

¹ Wagner's Handwörterb. der Physiol., ii, 1844, 628.

² Hermann's Handb. der Physiol., v, 1883, 279.

³ Phil. transact., London, i, 1842, 57.

osmosis, but is materially modified by the activity of the cells lining the convoluted tubule. It is assumed that the glomerulus furnishes the water and inorganic salts, while the distal convoluted tubule produces the specific organic constituents, together with an inconsiderable quantity of water. Thus, the character of this secretion depends in reality upon the activity of both groups of cells and varies with the differences in the composition of the blood, the blood pressure, and the velocity of the capillary blood-stream. This rather schematic presentation of these two theories, however, should not convey the idea that they are directly opposed to one another. They are not, because Heidenhain does not deny the occurrence of filtration, but merely amplifies this process by the secretory activity of the cells.

Facts Contradicting the Pure Mechanical Theory.—The kidney is one of the most vascular organs in our body, receiving about 150 c.c. of blood per minute for each 100 grm. of substance; moreover, its blood-supply is accurately controlled by a vasomotor mechanism contained in the renal and suprarenal plexuses.¹ The division of these fibers gives rise to a relaxation and injection of the blood-vessels of this organ, this change being associated as a rule with a copious flow of urine and a slight albuminuria. It is also a well-established fact that urinary secretion is closely dependent upon the blood pressure, because a fall in the latter is usually followed by a diminution in the quantity of the urine, and vice versa. While this relationship is entirely in accord with filtration, it can easily be shown that pressure is not the only factor here at work, because if the renal vein is temporarily obstructed, a procedure which must necessarily raise the intraglomerular pressure, the flow of urine stops altogether. In a similar way it has been shown that a partial obstruction of the venous return produces only a slight diminution in the rate of flow, which may immediately be increased by the administration of a diuretic. This latter fact is of importance, because Sollmann's experiments upon perfused excised kidneys have shown that the stoppage of the flow of urine following the ligation of the renal vein, may be caused by a mechanical obstruction of the uriniferous tubules caused by the distention of the entire organ. A dissociation between the renal blood-supply and the flow of urine may also be effected by the temporary ligation of the renal artery, or by the stimulation of the vagus nerve.² Almost directly thereafter the flow of urine ceases, as might be expected, but the flow does not regain its former value immediately upon the reestablishment of normal circulatory conditions, but in many instances only after an interval of from 30 to 60 minutes. Consequently, while it may be granted that the function of the kidney, like that of other organs, is closely dependent upon the blood-supply, it is easily apparent that some outside factor is here at work. In this connection, brief

¹ Bradford, *Jour. of Physiol.*, x, 1889, 358, Asher and Pearce, *Zeitschr. für Biol.*, lxiii, 1913, 83, and Burton-Opitz, *Jour. Exp. Med.*, xl, 1916, 437.

² Richards and Plaut, *Am. Jour. of Physiol.*, xlii, 1917, 592.

reference should also be made to the action of adrenalin which stops the secretion of urine in spite of the fact that it heightens the blood pressure. This discrepancy, however, is only an apparent one, because upon its entrance into the kidneys, this agent constricts the local blood-vessels and gives rise to an anemia which effectively blocks the activity of these cells.

Secondly, it might be mentioned that a certain secretory resistance does not retard the function of the renal cells but actually stimulates it. While it is true that urine is formed under a glomerular pressure of from 40 to 60 mm. Hg and a ureter pressure of about zero, the latter may be heightened considerably before the cells actually cease their function. The upper limit is reached at about 60 to 80 mm. Hg, *i.e.*, at a pressure less than half of that necessary to stop the secretion of saliva. The reason for their inability to raise the urinary pressure more decidedly above that prevailing in the capillaries, is due in largest part to the early occurrence of hydremia which indicates that the watery constituents of the urine escape into the interstitial spaces and are reabsorbed. Slight increases of the urinary pressure, on the other hand, invariably augment the activity of these cells.

Thirdly, mention should be made of those experiments which jointly establish the fact that the epithelial lining of the urinary tubules possesses true secretory properties. Heidenhain first attempted to prove this positively by injecting coloring material into the blood-stream of rabbits and demonstrating its presence in the cells of the urinary tubule by histological means. In order to eliminate the factor of pressure as much as possible, the spinal cord was cut previous to the injection. The vascular relaxation then ensuing gave rise to so low a blood pressure that practically no fluid came down the tubules. In all these cases, the indigo-carmin appeared in the form of blue granules within the cytoplasm of the rod-shaped epithelium, lining the convoluted tubules and ascending limb of the loop of Henle, but not in the cells of the glomeruli. In fact, some of these granules could also be detected in the lumen of the urinary tubule. This was invariably the case in all those animals whose spinal cord had not been divided before the injection. Evidently, the retention of the vascular tonus of the kidney tends to wash these granules rapidly out of the cells into the secretory duct.

More recently Schaffer¹ has confirmed these results by means of leuco-indigo-carmin, a colorless reduction derivative of indigo-carmin. This pigment remained colorless in the cells themselves, but appeared in its oxidized (blue) form in the lumen of the tubule. It could not be detected in the capsule of Bowman. Heidenhain has also shown that urate of soda is excreted by the lining cells of the tubules. In attempting to prove that the glomerulus acts independently of the convoluted tubule, Lindemann² sought to isolate this structure by

¹ Am. Jour. of Physiol., xxii, 1908, 323.

² Zeitschr. für Biol., xlii, 1902, 161.

injecting oil into the circulation, but since oil embolisms were then also found in the blood-vessels of the tubules, this method yielded no positive results, although it was evident that the tubular vessels ridded themselves of these embolisms much sooner than the glomerular vessels. Indigo-carmin injected at this time found its way in increasingly small quantities into the urine, indicating thereby a gradual opening up of the cells lining the convoluted tubules. The opposite condition may be produced in rabbits by means of sodium tartrate which substance gives rise to an inflammation or nephritis of the tubule.¹ If a solution of sodium chlorid and urea is then injected into the circulation, the chlorin enters the urine but not the urea. Obviously, the urea is ordinarily secreted by the lining cells of the tubule and not by those of the glomerulus.

FIG. 525.—SECTION THROUGH THE CONVOLUTED TUBULE (FROG) AFTER INJECTION OF TOLUIDIN.

L, Lumen of tubule; C, blood capillary. The lining cells show blue pigment and vesicles.

Fourthly, the secretory character of the tubular epithelium may be established as follows: In the frog it is possible to render either the glomerular or the tubular segment of the urinary tubule bloodless, because the kidney of this animal receives a double blood-supply. The one from the renal artery nourishes the glomerulus and the one from the renal portal vein, the tubule. Nussbaum² has shown that the ligation of the renal artery greatly diminishes the flow of urine. If urea is now injected into the dorsal lymph sac of this animal, a very considerable amount of this substance may be removed from the urine. Obviously, therefore, the urea must have found its way through the cells of the tubules. The successful outcome of this experiment requires a constant supply of oxygen in order to retain these cells in a proper condition of activity. This end can be accom-

plished by placing the frog in an atmosphere of oxygen. Contrariwise, sugar, peptone and egg-albumin, when injected into the blood-stream, do not enter the urine under these circumstances. These results have in the main been confirmed by Beddard.³ In addition, it has been shown that the cells of the convoluted tubule eventually degenerate when supplied only with renal-portal blood, because this blood is deficient in oxygen. The stimulating action of this gas upon the secretory power of the renal cells is also indicated by the experiments of Collis,⁴ which show that the perfusion of the frog's kidney with non-

¹ Underhill, Wells and Goldschmidt, *Jour. of Exp. Med.*, xviii, 1913, 347.

² Von Fürth, *Ergebn. der Physiol.*, 1902, 395.

³ *Jour. of Physiol.*, xxviii, 1902, 20.

⁴ *Ibid.*, xxxvii, 1908, 8.

oxygenated saline solution greatly diminishes the flow of urine. Contrariwise, the perfusion of this organ with oxygenated salt solution increases its quantity.

Fifthly, attention should be called to the fact that the cells lining the distal urinary tubule, possess all the essentials of secretory cells. Thus, vesicles may be seen to form within their cytoplasm, the contents of which are later on discharged into the lumen of the tubule.¹ Besides, Bowman has observed crystals of uric acid within the cells of the convoluted tubules of birds. Lastly, it is a well-known fact that the secretion of urine may be stimulated by means of various agents to which the name of diuretics has been given, and which in accordance with their stimulating action upon the cells themselves, may be placed in the same class with the lymphagogues, cholagogues and lactagogues. Their action may be tested most advantageously by perfusing the renal portal system of the frog with oxygenated salt solution to which either caffeine, urea, phloridzin, or sodium sulphate has been added. All these agents incite a copious secretion of urine as well as a very striking increase in the oxygen consumption of this organ. Very similar results may be obtained in mammals, but it is to be noted that the urine secreted under the influence of these secreto-gogues, is not at all like the blood plasma in its composition and also varies with the character of the diuretic employed. The vital activity of the renal cells is elucidated further by the fact that the sugar and proteins of the blood are normally retained in the body, whereas peptone and egg albumin, when injected into the circulation, are eliminated almost immediately. Moreover, the kidney possesses the power of abstracting urea from the blood, but does not excrete significant amounts of sugar, and this in spite of the fact that the latter substance is present in much larger quantities than the former.

Absorption from the Tubules.—While the preceding experiments fully disprove the pure filtration theory of urinary secretion, there is still another point embodied in Ludwig's theory which has given rise to much discussion. Reference is now had to the absorption of water from the urinary tubule to render the urine more concentrated than when first secreted. This reabsorption, it is claimed by Ludwig, is effected through the blood as well as through the lymph. In the first place, it must be admitted that the constituents of the urine may be made to pass in the reverse direction, as can be done by blocking the ureter and allowing the pressure in the tubules to rise well above that prevailing in the renal capillaries. Moreover, when substances, such as potassium iodid, are at this time injected into the pelvis of the kidney, they soon find their way into the blood where they may be recognized chemically. The only question to be decided is whether

¹ Gurwitch, *Pflüger's Archiv*, xci, 1902, 71; Courmont and André, *Jour. de Physiol. et path. gen.*, vii, 1905, 255; and Hüber and Königsberg, *Pflüger's Archiv*, cviii, 1905, 323.

this process as outlined by Ludwig and more recently by Cushny,¹ also takes place under normal conditions. In general, it may be said that this point has not been satisfactorily proven; at least, the evidence so far presented does not point toward a reabsorption of sufficient magnitude to account for the complete concentration of the freshly formed watery urine.

The factor of reabsorption has been emphasized in more recent years by Brodie and Callis,² and especially by Cushny. Possibly the strongest point against this contention is that the amount of water which would have to be reabsorbed from the uriniferous tubules, approximates the enormous value of 70 liters per day, but Cushny believes that this is not a convincing criticism, inasmuch as the secretion for each tubule would even then be only about 0.014 c.c. in the course of one hour. Ribbert³ has approached this problem by removing as extensive a portion of the tubules as possible, the contention being that if reabsorption actually takes place, a much more fluid urine should then be obtained. While this was actually the case, these results and their interpretation in favor of the absorption theory have been adversely criticized by Boyd⁴ and H. Meyer.⁵ The latter in particular lays stress upon the fact that the character of the urine after partial removal of the medullary substance more closely approaches that of an albumin-free filtrate. Furthermore, Gurwitsch⁶ has pointed out that the ligation of the renal portal system in frogs diminishes the quantity of the urine, as compared with that secreted by the normal organ on the opposite side. Consequently, if the tubules actually did absorb a large portion of the water of the newly formed urine, the abolition of their function should really give rise to a more copious and watery urine. As has just been stated, this is not the case. In addition, it must, of course, be evident that a process of secretion invariably necessitates two solutions, namely, the blood and the secretory product separated by an animal membrane, and Magnus, Sollmann and others have shown repeatedly that any interchange between these cannot be effected without the participation of the dissolved substances. For this reason, a slight reabsorption may be essential at times to equalize osmotic conditions, but not at all for the singular purpose of removing only the water.

"Modern" Theory of the Secretion of Urine.—The so-called "modern" theory of Cushny embodies the principles of urinary secretion as outlined by Ludwig, and in addition, a reabsorption of the water and inorganic constituents of the newly formed urine. The latter is effected by a vital activity on the part of the epithelium of the tub-

¹ The Secretion of Urine, London, 1917; also: Addis and Sheeky, *Am. Jour. of Physiol.*, xliii, 1917, 363.

² *Jour. of Physiol.*, xxxiv, 1906, 224.

³ *Virchow's Archiv*, xciii, 1883, 169.

⁴ *Jour. of Physiol.*, xxviii, 1902, 76.

⁵ *Marb. Sitzungsber.*, 1902.

⁶ *Pflüger's Archiv*, xci, 1902, 71.

ules. It is held that a large quantity of plasma is filtered through the glomerular vessels under the pressure of the blood and under exclusion of the colloidal proteins. The non-colloidal material being allowed to pass, owing to the permeability of the vessel-wall, imparts to the urine a concentration approximately equal to that of the blood. Consequently, the blood leaving the glomeruli, may be compared to a concentrated colloid solution which requires salts and water to reconvert it into its original form. This end the blood attains as it traverses the tubule by absorbing the constituents required by it from the glomerular filtrate. Those substances which the plasma must again obtain, are called *threshold substances*, while those which it does not need again, are designated as *non-threshold substances*. The latter remain in the urine to be excreted. Thus, urea must leave the body as long as any of it is present in the blood, whereas the urinary sugar must again pass into the blood, provided its concentration remains below the physiological limit.

This theory may well be employed to explain several perplexing points regarding the pathology of the kidney, particularly such as concern diuresis, albuminuria and the phenomena associated with the stagnation of the urine in consequence of urethral obstructions. In spite of this fact, however, it cannot be said that it rises above the dignity of a mere working hypothesis, because in view of the uncertain and contradictory character of the evidence presented in its favor, it seems risky to accept it as a truity. None seems sufficiently definite to allow of no other and, possibly, more correct interpretation. It appears, therefore, that the student who accepts Heidenhain's theory which does not wholly exclude the factor of glomerular filtration, cannot be considered as less "modern" than the one who adheres to the absorption-hypothesis. Thus, it may be said that water and salts, and even such substances as sugar, egg-albumin, peptone and hemoglobin when injected into the blood-stream, are mainly excreted by the glomeruli, whereas urea, uric acid, and the other organic constituents, together with small amounts of water and salts, are excreted by the epithelium of the uriniferous tubule. Neither process is accomplished by filtration alone, but embraces a definite vital element consisting of unknown physicochemical factors resident in the renal cells. Both processes are closely dependent upon the pressure and velocity of the renal blood flow. In this connection, it should also be mentioned that the existence of separate secretory nerves to the kidney has not been proved,¹ although it must be granted that the stimulation of the fibers constituting the renal plexus, profoundly affects the quantity and quality of the urine. These results, however, may be due wholly to vasomotor influences.

Diuresis.—The diuretics produce their characteristic effect in two ways, namely, by augmenting the secretory pressure and concentra-

¹ Asher and Pearce, *Zeitschr. für Biol.*, lxiii, 1913, 83; and Pearce and Carter, *Am. Jour. of Physiol.*, xxxviii, 1915, 350.

tion of the blood, or by furthering the activity of the renal cells. Consequently, either the glomerulus or the tubule may be involved in this process. Thus, we might say that digitalis enhances the circulatory conditions, because it stimulates the cardiac musculature and raises the tonicity of the vascular channels. Caffeine possesses a similar action.¹ It is evident, however, that a mere increase in the vascularity or a passive injection of the renal capillaries does not give rise to a flow of urine. Another way in which the secretory conditions might be altered, is to change the osmotic pressure of the blood. For example, if a hypertonic solution of sodium chlorid is injected into the circulatory system, the osmotic pressure of the blood is increased, and fluid is drawn into the vascular channels from the lymphatics until it acquires a lower osmotic pressure.² This condition is called *hydremic plethora*. It follows then that the renal blood flow is more rapid and forceful, a change which greatly favors the transudation of the excess of fluid through the renal capillaries. The same effect may be produced intentionally by the ingestion of large quantities of water or by means of dialyzable substances, such as sodium sulphate, sodium or potassium bicarbonate, the acetate, citrate or bitartrate of potassium, liquor ammonii acetatis, liquor ferri et ammonii acetatis, urea, and dextrose. The most efficient of these are the bicarbonates and potassium acetate. Urea and dextrose may act chiefly as direct stimulants to the renal cells, but also, in a measure, by changing the osmotic conditions. Pituitary extract seems to possess a direct action upon the cells although its action upon the circulatory system cannot be excluded.

A more detailed explanation of diuresis cannot be given unless resort is taken to the well-conceived but still hypothetical absorption "theory." If the polyuria of diabetes mellitus is taken as an example, it might be said that the kidney is quite unable to concentrate the urine against the concentrated sugar-urine in the tubules. In accordance with the preceding discussion, this would imply that sugar becomes a "non-threshold" substance, owing to the presence of sugar in the blood in amounts greater than the optimum.

Albuminuria.—While the proteins of the blood do not enter the blood under normal conditions, their escape cannot be prevented if the permeability of the glomerulus is increased. A condition of this kind develops in acute nephritis and cardiac failure. The quantity of the urine is then usually diminished, but the question of whether this disease remains confined to the glomeruli or also involves the tubules, cannot be decided with certainty. Theoretically, however, we might expect to obtain a glomerular as well as a tubular nephritis. In the chronic type of this disease the urine retains a low specific gravity and viscosity³ and, using the absorption hypothesis as a basis,

¹ Löwi, Arch. für exp. Path. und Pharm., liii, 1905, i.

² Gottlieb and Magnus, *ibid.*, xlv, 1901, 223.

³ Burton-Opitz and Dinegar, Am. Jour. of Physiol., xlvii, 1918, 220.

it might be said that this condition is dependent upon an impairment of the resorbing mechanism.

Let us also remember that the removal of one kidney is not followed by any untoward results, because the opposite organ then enlarges and continues to do the work previously accomplished by the two. The extirpation of both kidneys, however, proves fatal invariably, the animal dying a few days later of uremic poisoning. The same results follow the ligature of both renal arteries.¹ While the conditions of anasarca, ascitis, and others, would furnish many points of physiological interest, they more properly belong into the field of general pathology.

CHAPTER XC

THE EXPULSION OF THE URINE. MICTURITION

The Function of the Ureter.—The duct of each kidney, or ureter, is a muscular tube measuring about 30 to 45 cm. in length. It begins above at the pelvis and terminates below in the wall of the bladder. It is lined by mucous membrane and consists of an inner circular coat of smooth muscle tissue and an outer coat of fibrous tissue. As the small globules of urine escape from the different collecting tubules, they are retained at first in the pelvic cavity until this reservoir has become sufficiently distended. A reflex is then set up which gives rise to peristaltic waves which travel slowly in the direction of the bladder, each contraction forcing a small amount of urine ahead of it. These waves recur at rather regular intervals and increase in frequency as larger amounts of urine are secreted. Their number is usually 3 to 6 in a minute and their rate of progression 2 to 3 cm. in a second.²

The activity of the ureter is controlled by nerve fibers derived from the renal plexus as well as from the hypogastric nerves. Their central segments, however, are said to be free from them, although ganglion cells have been detected throughout their entire length. In accordance with this rather deficient nerve-supply, Engelmann³ has formulated the theory that these rhythmic contractions are of myogenic origin. This view finds additional support in the fact that even excised portions of the ureter show a peristaltic activity which may be greatly increased by immersing them in warmed saline solution. Equally convincing data, however, might be submitted in favor of the neurogenic theory, and hence, no definite statements can be made at this time regarding

¹ Pilcher, Jour. Biol. Chem., xiv, 1913, 387.

² Heidenhain, Archiv für mikr. Anat., 1874; and Protopow, Pflüger's Archiv, lxvi, 1897.

³ Pflüger's Archiv, ii, 1869.

this matter. The pelvic segment of the ureter is undoubtedly well equipped with nerve fibers and it appears that this portion acts as the pace-maker for the lower segments. Experimentally, however, it is possible to evoke peristalsis in any part of this organ. Since smooth muscle tissue is seldom richly supplied with nerve tissue, the relatively "nerve-free" central portion might normally be dependent upon influences conveyed to it from the pace-maker through the agency of the aforesaid ganglion cells.¹

The Urinary Bladder.—The bladder is composed of a mucous, submucous, muscular and serous layer. Its muscular coat contains an outer longitudinal, a middle circular, and an inner anastomosing or oblique layer of fibers. The fibers of the first pass in an almost direct line from the fundus to the urethra, where some of them become attached to the pelvis as the pubovesical muscle. Posteriorly, the strands end, in the male, in the prostate and, in the female, in the urethral-vaginal septum. The median coat is much thicker and consists of fibers arranged transversely to the long axis of the organ. At the cervix, this layer is materially strengthened, forming here the internal sphincter vesicæ. Farther outward and enveloping the root of the urethra, is a second sphincter which is composed of striated muscle tissue, and is usually designated as the external sphincter or sphincter urethræ. The inner coat of muscle tissue consists of obliquely arranged fibers which are distributed in an irregular manner and permeate the different layers.

As each ureter continues to empty small quantities of urine into the fundus of the bladder, its walls are forced outward more and more until they have attained a physiological degree of distention. A contraction of the musculature then ensues which drives the urine through the relaxed sphincters to the outside. Under ordinary conditions, therefore, the peristaltic waves of the ureters need not overcome a considerable resistance and their power is more than ample to force the urine into the fundus. But a regurgitation of the urine into the ureters is quite impossible even during the interims, because the orifices of the ureters are firmly closed. This end is not accomplished by special sphincters, but in an indirect way by the distention of the walls of the bladder. Inasmuch as the ureters perforate the latter in an oblique direction and open by means of slit-like orifices, the gradual filling of the bladder must cause the lip-like margins of these openings and neighboring segments of the ureters to become firmly approximated. Consequently, the greater the internal pressure, the more firmly will these orifices be closed. In general, therefore, it may be said that three factors are at work to prevent the regurgitation of the urine, namely, gravity, the peristaltic action of the ureters, and the mechanical closure of their orifices by the distention of the walls of the bladder.

The foregoing discussion also shows that the high pressures which

¹ Lucas, *Am. Jour. of Physiol.*, xvii, 1906, 392.

are developed at times within the bladder during its periods of contraction, cannot possibly interfere with the vascular supply nor the secretory function of the kidneys.¹ Very different conditions, however, arise if the pressure in the ureter itself is raised excessively, a condition commonly associated with the stagnation of the urine in consequence of renal calculi. A very decided reduction in the blood flow through the corresponding kidney then results which cannot remain without effect upon its secretion.

Physiologically, the bladder must be considered as a hollow muscular organ, the contraction of which places its contents under a considerable pressure.² Since the orifices of the ureters are closed, the pressure so developed must be directed toward the internal and external sphincters. The resistance of the latter, however, cannot be overcome by pressure alone, and hence, the voiding of urine or act of micturition must also necessitate the relaxation of these bands of muscle tissue, the inner one by reflex action and the outer one volitionally. A third factor at work during this process is the abdominal press. It will be remembered that the latter consists in an inspiratory action which is immediately followed by a closure of the laryngeal orifice and a contraction of the abdominal muscles and diaphragm. The increase in the abdominal pressure produced thereby is propagated unto the pelvic organs and favors micturition as well as defecation. In most instances, however, it is not brought into play until the final stages of these acts.

Under ordinary conditions, micturition does not result until the pressure in the bladder has risen to about 150 mm. H_2O , *i.e.*, at a time when this organ has been distended sufficiently to contain between 230 and 250 c.c. of urine. To begin with, of course, the pressure increases very slowly, owing to the constant relaxation of the walls of the bladder. Eventually, however, as the tissues have about attained their maximal degree of stretching, the pressure rises more rapidly and finally evokes a series of slight rhythmic oscillations which are soon succeeded by more forcible contractions. But, much depends upon the rapidity with which the bladder is being filled, because a slow influx of urine enables the different muscle fibers to lengthen more gradually, while a more rapid influx causes them to react antagonistically by tonic or rhythmic contractions, thereby evoking micturition much sooner. Furthermore, since the external sphincter is under the control of the will, the forceful contraction of this ring of muscle tissue may overcome these reflexes, at least for a short time. When aided by the abdominal press, a pressure of 2 m. H_2O may be produced.

The Nervous Control of the Bladder.—The reflex center for micturition is situated in the lumbosacral segment of the spinal cord, whence connections are formed with the higher centers. In this way, volition

¹ Burton-Opitz, Pflüger's Archiv, cxxiii, 19.

² Rehfisch, Virchow's Archiv, xl, 1897, iii; also: Mosso and Pellacani, Arch. ital. de biol., i, 1882, 291.

and various afferent impulses may be brought to bear upon this reflex mechanism. Thus, we have previously found that micturition may also be evoked by associations resulting in consequence of visual and auditory impressions, such as the sight or sound of running water. Secondly, the action of the simple center may be inhibited or accelerated by volition. In the latter case, however, the impulses seem to be concentrated upon the sphincter mechanism and upon those perineal muscles which normally aid in the closure of the urethra. Contrariwise,

FIG. 526.—NERVE SUPPLY TO BLADDER OF CAT. (*Nawrocki and Skabitschewsky.*)

the relaxation of these sphincters may be hastened by the contraction of the abdominal muscles; in fact, it is held by some investigators that even the involuntary muscle tissue of the bladder is partially under the control of the cortex of the cerebrum. This view is based upon the fact that the destruction of the crus cerebri in animals whose abdomen had been opened, gives rise to a contraction of the bladder.

Since the local mechanism of micturition requires efferent impulses which, on the one hand, lead to a contraction of the musculature of

the bladder, and, on the other, to a relaxation of the sphincter, two separate nerve paths must be provided for. According to Langley and Anderson,¹ one of these arises in the four upper lumbar nerves and the other, in the second and third sacral nerves by way of the visceral nerves of the pelvis, the *nervi erigentes*. The former eventually terminate in the bilateral inferior mesenteric ganglion, whence a new relay of fibers is formed which extends in the form of two nerves, the hypogastric nerves, into the pelvis on each side of the rectum. They terminate finally at the base of the bladder in an extensive ramification which is known as the hypogastric plexus. From here these fibers ascend to the fundus of the bladder. The second set of fibers passes from the second and third sacral nerves directly to the hypogastric plexus, and hence, they do not first enter the sympathetic system. Their relay stations lie in the aforesaid plexus and in the walls of the bladder itself. The afferent impulses from this organ select chiefly these visceral fibers of the pelvis in reaching central parts.²

This brief enumeration shows that the hypogastric plexus is supplied with sympathetic fibers from the lumbar cord and with parasympathetic fibers from the sacral cord. As far as the individual action of these fibers is concerned, further investigations are needed to be able to cite definite results. All physiologists, however, are agreed that the excitation of the sacral fibers on either side produces a strong contraction of the bladder, leading to the relaxation of the sphincters and the discharge of the urine. But, the question whether these nerves actually contain inhibitory fibers for the sphincters, has not been definitely settled. Fagge,³ for example, claims that they do not and that the relaxation of the sphincters takes place indirectly in consequence of the high intravesical pressure. The function of the hypogastric nerves has not been clearly established, because it is not the same in all animals. In the dog, their stimulation leads to a strong contraction of the musculature around the base of the bladder, whereas in the cat and rabbit this procedure gives rise to an inhibition. It appears, however, that they are never without motor fibers for the sphincter vesicæ and the constrictor tissue of the urethra.

¹ Jour. of Physiol., xix, 1895, 71; also Stewart, Am. Jour. of Physiol., xxx, 1899, i.

² Nawrocki and Skabitschewsky, Pflüger's Archiv, xlix, 1891, 141.

³ Jour. of Physiol., xxviii, 1902, 305.

CHAPTER XCI

THE COMPOSITION OF THE URINE

General Characteristics of Urine.¹—The urine of man is a clear, fluorescent fluid, the *color* of which varies from light yellow to dark yellow in accordance with its content in pigmentous material. The latter consists chiefly of *urochrome*, which is composed of 11.1 per cent. of nitrogen and 5 per cent. of sulphur, and is in all probability derived from protein. *Urobilin*, another pigment, is present in normal urine in only very small quantities. It is derived from the coloring material of the bile which is converted in the intestines into stercobilin. While the latter leaves the body principally in the feces, some of it is reabsorbed to be finally excreted in the urine. Its mother-substance, known as urobilinogen, is present in somewhat greater quantities and is easily oxidized into urobilin proper. The pink coloring material of the urates is *uroerythrin*. A trace of *hematoporphyrin* is also present normally.

The *odor* of urine depends upon the quality of the food ingested. When meat, bread and butter are taken, it is not at all unpleasant. A most peculiar odor is imparted to it by asparagus. To the *taste* urine is bitter and salty. The *quantity of urine* varies considerably, and depends upon the intake of water and the proportion of it which is excreted through other channels, such as the intestines, sweat glands and respiratory passage. Under ordinary conditions, from 1400 to 1800 c.c. are voided in the course of twenty-four hours, the smallest portion of this amount being excreted during the night. If a reverse relationship exists so that the person must micturate during the night, suspicions of renal disease should be aroused, but naturally, only if moderate amounts of water and other fluids have been taken on the evening preceding.

The *specific gravity of the urine* varies greatly in different persons as well as in the same person at different times of the day. The chief factor tending to vary its value is the proportion of water to the amount of solids ingested, and the relationship between the activity of the kidneys and that of the other excretory channels. Under ordinary conditions, values between 1.015 and 1.025 are encountered, while a constant value of 1.010 and less would point toward the presence of hydruria, and one of 1.030 and over, toward diabetes. Temporary variations of this kind, however, are common and may easily be produced by an intake of large quantities of water or by profuse sweating.

¹ For a more detailed discussion the reader is referred to Mathew's *Biological Chemistry*, Hamburger's *Osm. Druck and Jonenlehre*, and Oppenheimer's *Handb. der Biolog. Chemie*.

The *viscosity of urine* is normally 1.2 as great as that of distilled water at 37° C. While blood freezes at -0.56°C ., *urine freezes* at -1.0 to -2.5°C . If very dilute, the freezing point may lie at 0.075°C ., and if very concentrated at -5°C .

The *reaction of the urine* of man and the carnivora is acid to litmus and phenolphthalein. This is due to the fact that neutral constituents of the food are eventually transformed into acid end-products, the sulphur of the proteins giving rise to sulphuric acid, and the phosphorus of lecithin to phosphoric acid. An ingestion of large quantities of vegetables and fruits, however, will make it alkaline and turbid, owing to the precipitation of earthy phosphates. In the herbivora, the urine is alkaline, because their food embraces fruits and vegetables which contain salts of dibasic or polybasic acids, such as acid potassium malate, citrate, acetate and tartrate. The oxidation of these bodies during metabolism gives rise to carbonates. Some of the carbonic acid leaves the body through the lungs, whereas their bases are excreted in the urine as alkaline carbonates. For this reason, the urine of these animals frothes on addition of an acid. Furthermore, if these animals are starved, their urine becomes acid, because they then live upon their tissues and are converted, so to speak, into carnivorous animals. This is also true of man, because the withholding of fruits and vegetables removes all possibility of the urine becoming alkaline. In disease, it is more generally acid, this change being due in most instances to the restriction of the diet. With the increase in acidity, the excretion of ammonia is usually augmented.

The *composition of the urine* differs somewhat with the type of food ingested and the quantity of water eliminated through this channel. In general, however, it may be said to contain 60 grm. of solids, of which 25 grm. are in the form of inorganic and 35 grm. in the form of organic substances. Thus, an adult man on a mixed diet yields about 1500 c.c. of urine in a day which shows the following composition:¹

Inorganic substances		Organic substances	
Sodium chlorid.....	15.0 grams	Urea.....	30.0 grams
Sulphuric acid.....	2.5 grams	Uric acid.....	0.7 grams
Phosphoric acid.....	2.5 grams	Creatinine.....	1.0 grams
Potassium.....	3.3 grams	Hippuric acid.....	0.7 grams
Ammonia.....	0.7 gram	Other constituents.....	2.6 grams
Magnesia.....	0.5 gram		
Lime.....	0.3 gram		
Other constituents.....	0.2 gram		

THE INORGANIC CONSTITUENTS OF URINE

Chlorids.—The inorganic or mineral constituents of urine consist principally of chlorids, phosphates, sulphates and carbonates of sodium, potassium, ammonium, calcium, and magnesium. The total amount

¹ Mosenthal, Arch. Int. Med., xvi, 1915, 733.

of these salts varies between 19 and 25 grm. per day, of which sodium chlorid is the most abundant, because it is excreted in amounts of 10 to 16 grm. in a day. Evidently, the chlorids of the urine are derived almost wholly from the chlorids of the food and hence, their amount must vary very closely with the character of the material ingested. If the latter is rendered relatively chlorin free, the chlorids may disappear almost completely from the urine, although the blood retains its normal composition in this regard. Quite similarly, the intake of large quantities of table salt raises the chlorin content of the urine. It is diminished in certain diseases, such as acute pneumonia.

Sulphates.—The sulphates of urine are principally those of potassium and sodium, but since the salts of sulphuric acid, owing to their bitter taste, etc., do not form an important constituent of our food, the sulphates in the urine are derived almost exclusively from the oxidation of the sulphur of the proteins. The nitrogen of these substances leave the body chiefly as urea, while their sulphur constituents are converted into sulphuric acid which is passed into the urine in the form of sulphates. Consequently, the output of sulphates may be employed as an index of protein metabolism, in the same way as urea. The average daily output of sulphates varies between 1.5 and 3.0 grm.

In addition to the sulphates of the alkaline metals, urine also contains a small proportion of them in the form of conjugated or ethereal sulphates (10 per cent.), principally as phenyl sulphate and indoxyl sulphate of potassium. The latter originates in largest part in the putrefactive processes within the intestine, chiefly from indole, and as it yields indigo when treated with certain reagents, it is usually called indican. The presence of this substance is of some importance, because it allows us to estimate the intensity of intestinal putrefaction and the power of our body to convert these poisonous derivatives into the innocuous ethereal sulphates. A small proportion of the sulphur contained in urine, is present as neutral sulphur representing its unoxidized form.

Carbonates.—These salts are present only in alkaline urine, and are represented by the carbonates and bicarbonates of sodium, calcium, magnesium, and ammonium. They arise from the carbonates of the food, and must, therefore, be most evident in herbivora and vegetarians. A urine of this kind becomes cloudy on standing, owing to the precipitation of its carbonates, chiefly calcium carbonate, and also phosphates.

Phosphates.—These salts are derived partly from the phosphates of the food and partly from the oxidation of the organic phosphorus-containing bodies of the tissues, such as nuclein, lecithin, etc. Their daily excretion varies between 1.0 and 5.0 grm., calculated as P_2O_5 , and is almost wholly dependent upon the phosphate content of the food. Thus, if much calcium or magnesium is present in the latter, they are excreted in the feces as calcium and magnesium phosphate, sometimes as much as 30 per cent. of the total choosing this medium

for leaving the body. The remainder exists in the urine as mono- and disodium hydrogen phosphate, the amount of each varying with the reaction of this medium. If neutral or alkaline, a deposit of earthy phosphates results which may immediately be cleared up by the addition of acid. This condition generally arises after a copious vegetable diet, when a large amount of disodium hydrogen phosphate is produced. Quite similarly, an abundant ingestion of protein substances, gives rise to an acid urine, owing to the formation of sulphuric and other acids. In the latter case, there is a greater formation of phosphoric acid and production of monosodium hydrogen phosphate.

On standing, the urine assumes an alkaline reaction, owing to the conversion of the urea by the micro-organisms into ammonium carbonate. Under these circumstances, a creamy white precipitate is formed which consists of triple phosphate or ammonium-magnesium phosphate, and stellar phosphate or calcium phosphate. It should be remembered, however, that even normal human urine contains a small quantity of ammonia, *i.e.*, from 0.6 to 0.8 grm. in a day. This amount may serve as an index of the excess of acids over bases which are to be excreted. While it is possible to vary this amount artificially, for example, by the administration of mineral acids, any increase during the normal ingestion of food invariably signifies that abnormal acid substances are formed in the body. This is the case in diabetes mellitus, a disease in the course of which the fatty acids accumulate in consequence of their diminished oxidation. This accumulation must necessarily lead to a rise in the ammonia content of the urine.

THE ORGANIC CONSTITUENTS OF URINE

Urea or Carbamide.—The greatest amount of the organic material in urine is made up of nitrogenous bodies which are derived from the proteins of the food. We have seen that the substances are broken up in the intestinal canal into their amino-acids which after their absorption are either converted into the proteins of the tissues or are diamidized. In the latter case, the principal portion of the carbon, oxygen, and hydrogen is oxidized to form CO_2 and water, whereas the smaller portion is combined with nitrogen to form urea, ammonia, uric acid, and other bodies. This same fate awaits the tissue-proteins which are constantly broken down and replaced by new material. It has also been pointed out above that by far the largest amount of the nitrogen of the food is excreted in the urine, and that only a small portion of it enters the feces or is lost in the sweat. Consequently, the total nitrogen content of the urine gives in a fair way the total amount of nitrogen ingested, because under ordinary conditions, the body is in nitrogen-equilibrium and its N-ingo equals its N-outgo. This relationship, however, does not hold true when the body is growing and needs nitrogenous material for the construction of its cells. It may also be disturbed for a time for other reasons. Thus, a reduc-

tion in the amount of the proteins ingested finally causes a diminution of the body-proteins, which in turn are drawn upon later on to make good the loss in the intake. Quite similarly, any increase in the protein content of the food gives rise to an increase in the nitrogen of the urine. The nitrogen metabolism of the body, however, cannot be estimated precisely unless a comparison is made between the total nitrogen of the urine and the amount of nitrogen ingested, because only when both factors are known is it possible to determine the character of the intermediary processes.

The most important nitrogenous constituent of urine is urea. Formerly thought to be produced in the kidneys, it is now a well established fact that it arises elsewhere in the body and is brought to these organs in the form of a rather complete precursor. The renal cells, therefore, merely remove this product from the blood by virtue of a peculiar selective power. We know this to be true, because the formation of urea and other waste products of this type continues even after the kidneys have been extirpated or have been rendered functionally useless by disease. This substance then accumulates in the blood and gives rise to the condition of uremia. It should be noted, however, that the poison acting at this time, is not the urea nor any other normal constituent of urine, but some intermediary product of protein catabolism. The question pertaining to the place of origin of this substance seems to have been decided in favor of the liver, because:

(a) The removal of this organ in mammals proves fatal owing to the accumulation of certain catabolic substances. This is indicated by the gradual diminution of the urea content of the urine. A similar effect may be produced by the establishment of an Eck fistula, the urea of the urine then being lessened and the ammonia increased.

(b) The extirpation of the liver in the frog and allied animals brings about a substitution of the urea by ammonia.

(c) Such diseases as cirrhosis and yellow atrophy of the liver are characterized by a similar change. In the latter case, the amino-acids, such as leucine and tyrosine, appear in the urine, because they escape further reduction in the liver and pass directly into the urine.

(d) If amino-acids, such as glycine, leucine, arginine, and others are administered by the mouth or are injected into the blood-stream, the urea excretion is increased.

This view, that urea is the result of a conversion of the amino-acids by the cells of the liver, is also strengthened by the fact that some of these bodies may be made to undergo this change in the test tube. In the case of arginine, Kossel and Dakin¹ have found that it consists of a urea radicle and a substance known as ornithine. On hydrolysis it splits into urea and ornithine. This same reaction is supposed to occur in the liver under the influence of arginase, the arginine then being split up into simpler compounds which are again combined

¹ Zeitschr. für Physiol. Chemie, xlii, 1904, 181.

differently into urea. Schroder¹ has shown that one of these simple compounds, although not the principal one, is ammonium carbonate. Thus, it may be concluded that urea is a synthetic product of the liver cells.

In accordance with our previous discussion, urea may be regarded as partly exogenous, and partly endogenous, because it is derived, on the one hand, from nitrogenous bodies which have been absorbed but have not become intimate constituents of the tissue cells, and, on the other, from bodies which have been discharged by the cells after they have previously formed a part of them. In other words, urea finds its origin in the circulating proteins, as well as in the tissue proteins. It may then be reasoned that a person in nitrogen-equilibrium discharges only a small and rather constant amount of tissue proteins and that, therefore, the endogenous urea must possess a small and constant value. Contrariwise, it may be assumed that the amount of the exogenous urea is much larger and variable, because it is taken from the variable and excess quantities of proteins ingested. It is true, however, that the endogenous variety may also undergo marked alterations, for example, in fevers and other pathological conditions causing a rapid destruction of the tissue proteins.

Although subject to variations for reasons just stated, the amount of urea excreted in the course of a day is usually given as 33 to 35 gm., provided about 100 to 120 gm. of protein are ingested.² Its amount becomes greatest three hours after a mixed meal and may constitute as much as 90 per cent. of the total nitrogen if large quantities of protein are ingested. Upon a low protein diet, such as has been advocated by Chittenden, the urine shows a nitrogen-content considerably below that ordinarily regarded as normal. The proportion of urea may then be diminished to 60 per cent., because its chief source, the exogenous nitrogen, has been eliminated in part. Muscular exercise does not affect the urea output, showing that the energy is derived in this case from the combustion of non-nitrogenous substances, chiefly the carbohydrates. Some authors also state that a direct relationship exists between the rate of urine secretion and the amount of urea in the blood and urine, and claim to be able to evaluate the functional power of the kidney by a comparison of these factors.³

Urea possesses the formula $\text{CO}(\text{NH}_2)_2$ and is isomeric with ammonium cyanate (NH_4CNO). This implies that it has the same empirical but not the same structural formula. This substance was employed by Wöhler in 1828 in the synthetic preparation of urea. Crystals of this substance may be obtained by warming potassium cyanate together with ammonium chlorid. In this form, urea is readily soluble in water and alcohol and possesses a salty taste and a neutral reaction to litmus. On treatment with nitric acid, the nitrate of urea is formed

¹ Archiv für exp. Path. und Pharm., xv, 1882, 364.

² Addison and Watanabe, Jour. Biol. Chem., xxvii, 1917, 381.

³ Ambard and Weil, Physiol. norm. et path. des reins, Paris, 1914.

($\text{CON}_2\text{H}_4\cdot\text{HNO}_3$), and on treatment with oxalic acid its oxalate ($\text{CON}_2\text{H}_4\cdot\text{H}_2\text{C}_2\text{O}_4 + \text{H}_2\text{O}$). Urea melts at 130°C ., undergoing finally a decomposition which yields ammonia, biuret and cyanic acid, the latter being polymerized to cyanuric acid. On hydrolysis by means of heating with strong acids or alkalies, it yields carbon dioxid and ammonia.

Ammonia.—The urine of man and the carnivora contains a small quantity of ammonium salts which serve as a means of transfer for the acid radicles which have been ingested or have been formed in the body. The chief source of these salts is the ammonia of the blood, derived from the nitrogenous portion of the diamidized amino-acids. This ammonia is carried to the liver where urea is synthetized, but some of it escapes and reaches the kidneys where it slips through into the urine. Some of it is also derived from the ammonium salts ingested from the ammonia produced in the course of the intestinal putrefaction of the proteins. In the body, it exists as ammonium carbonate which is the precursor of urea. It is for this reason that so little of it circulates, but when mineral acids are administered, or when excessive quantities of acids are produced, as in diabetes mellitus, the body makes use of the ammonia as a base and an extra amount of it appears in the urine. An excess of alkali, on the other hand, causes it to be transferred into urea and to disappear as such from the urine. This accounts for the fact that it is not present in the urine of vegetarians nor in that of the herbivora. Ordinarily, the daily output of ammonia-nitrogen varies between 0.3 and 1.2 gm., the average being 0.7 gm., or 3.5 per cent. of the total amount of nitrogen.

Acidosis.—It has been known for some years that the urine of diabetics is loaded with acetone, diacetic acid and β -oxybutyric acid. It was supposed at first that these bodies are derived from glucose, because they are present in glycosuria, but it is now known that they are the result of a disordered process of breaking down the fats. Ordinarily, this foodstuff is converted into carbon dioxid and water, but in certain abnormal conditions there is produced β -oxybutyric acid, then diacetic acid and lastly, acetone. Since a small amount of acetone is normally present in urine and especially after the ingestion of butter consisting of the lower fatty acids, and since none of these substances is poisonous, except in enormous doses, it may be asked why they cause such serious disturbances when formed in the course of metabolism. Briefly, the answer is this: Fats are converted into these abnormal acids instead of into carbon dioxid and water whenever the tissues are unable to obtain sugar from the blood. The blood is normally alkaline and the functions of the tissues are adapted to this particular reaction. In consequence of the production of diacetic and especially of β -oxybutyric acid, its alkalinity is greatly reduced. The functional disturbances then ensuing constitute the condition of acidosis. It would seem, therefore, that an artificial supply of alkalies should place the body in a position to withstand the presence of these

acids.¹ This is true to a large extent, because even the body attempts to remedy this defect by calling to its defense first its reserves of sodium and potassium and lastly, and most effectively, large quantities of ammonia. We have seen that the proteins turn their effete nitrogen into ammonium carbonate and carbamate which are then converted into urea in the liver. When the body employs this ammonia as a defense, it combines it with the diacetic and β -oxybutyric acids and does not convert it into urea. Consequently, the ammonia escapes in this case into the urine as ammonium diacetate and ammonium β -oxybutyrate. Finally, when the body has reached its limit in this regard, the normal alkalinity of the blood can no longer be maintained and dyspnea, collapse and coma result.

Creatin and Creatinin ($C_4H_7N_3O$).—On a diet free from meat, creatin is excreted in amounts varying between 7 and 11 mgr. per kilogram of body weight. Folin² regards it as a criterion of the intensity of the endogenous nitrogenous metabolism and believes that it is formed in the liver and not in the muscles which usually contain it in abundant amounts. Any gross variation from the amount just given signifies an accumulation of this substance in the blood. Melanby claims that creatinin is derived from certain derivatives of protein catabolism in the liver and is then conveyed from this organ to the muscles, where it is converted into its anhydride, creatin. As soon as this tissue becomes saturated with this substance, creatinin is excreted in the urine, and hence, a renal deficiency would invariably be followed by an accumulation of the latter in the blood.

Uric Acid ($C_5H_4N_4O_3$).—The quantity of uric acid normally present in the urine of man is small. It varies between 0.3 and 1.2 gm. per day or between 0.02 to 0.10 per cent. This amount may be derived from the ordinary purin metabolism of the body (endogenous) or from the food ingested (exogenous). For this reason, it may readily be increased by the ingestion of food rich in nucleins, or substances containing the purin bases in a free state. Since the human body does not possess the power of destroying any of the uric acid, it must be excreted as such in the urine. This being the case, one of the earliest symptoms of renal insufficiency is the increase of uric acid in the blood. The reason for this is not quite clear, unless it is taken into account that its salts are the least soluble of any excreted in the urine. This also explains the fact that urine when cooled, yields a pink deposit of urates. Uric acid is present in large amounts in the urine of birds and snakes, forming here acid ammonium urate.

The *purin bases* are largely transformed into uric acid and only their residue appears in the urine. Only traces of *hippuric acid* are present under normal conditions (0.7 gm. per day), but the ingestion of fruits and vegetables may raise it to 2 gm. per day. *Amino-acids*

¹ Von Noorden, "Diabetes Mellitus," Wright and Sons, Bristol, 1906.

² Am. Jour. of Physiol., xiii, 1905, 66 and Jaffé, Zeitschr. für physiol. Chemie., xlviii, 1906, 430.

may also be present in amounts equalling 1.5 per cent. of the total nitrogen.¹ Aromatic oxyacids, such as phenol, indoxyl and skatoxyl, are normally present in varying amounts, and serve as an indication of the putrefactive decomposition of the proteins in the large intestine. Ordinarily, the body protects itself by oxidizing them and combining them to sulphuric acid to form the ethereal sulphates.

¹ Van Slyke and G. M. Meyer, *Jour. Biol. Chem.*, xvi, 1913, 197.

SECTION XXIX

ANIMAL HEAT

CHAPTER XCII

THE PRODUCTION AND DISSIPATION OF HEAT

Thermometry and Calorimetry.—Inasmuch as all chemical processes require an optimum degree of temperature for their completion, it may be concluded that the assimilation and dissimilation of the different foodstuffs cannot be effected in the absence of a definite measure of heat. This heat may be derived from two sources, namely, as radiating or bound energy from without, or as energy liberated in the course of the different chemical changes to which the tissues and organs of the body are subject. Under ordinary circumstances, the latter form of heat is of by far the greatest functional importance to us, but its detection and actual measurement presents many rather unexpected difficulties, so that very sensitive instruments must be employed in order to prove its liberation. In the case of such structures as the muscles and glands, we make use of the so-called thermo-electric elements which consist of two dissimilar metals, such as German silver and iron, soldered together. One of these is placed in some indifferent tissue or in the blood-stream, while the other is inserted in the organ, the temperature of which is to be determined. If the binding posts of these two pairs of elements are then connected with a galvanometer, it will be found that the least production of heat at the point of soldering gives rise to a difference in potential which will be accurately indicated by the deflection of the galvanometric needle.

It is evident, however, that this method cannot be employed to determine the total heat-production of an animal nor its body-temperature, because this method must necessarily remain restricted to single and separate organs. Should we desire to determine the temperature prevailing within the body of an animal we must, of course, make use of a *thermometer* which is inserted in any one of its cavities or recesses and is allowed to remain there until the mercurial indicator has assumed a stationary position.¹ It must be evident, however, that thermometry merely serves as a means of determining the temperature existing at any particular moment and cannot yield data regarding the total amount of heat produced by the animal. Should we wish to

¹ The thermometer was devised by Galilei in 1603. The first thermometric determinations upon man were made by Sanctorius in 1626.

ascertain the latter factor, it becomes necessary to employ an instrument which is known as the *calorimeter*,¹ and presents itself in the form of two modifications, designated as the water-calorimeter and air-calorimeter. In either case, this apparatus consists of a central compartment in which the animal is kept, and a narrow outer compartment which is filled either with water or with air. Externally its walls are covered with a heavy layer of some non-conductile material to prevent all losses of heat. The heat liberated by the animal is then

FIG. 527.—WATER CALORIMETER. (Reichert.)

A, Inner compartment for animal; SH, space filled with non-conductile material; ENT and EXT, tubes for the respiratory air; CT, thermometer in jacket filled with water; S, stirrer to equalize the temperature of the water.

transmitted to the water, the temperature of which is read off by means of a stationary thermometer.² In the case of the air calorimeter, the heat evolved by the animal gives rise to an expansion of the air contained in the outer compartment, which is then transferred by calculation into degrees of heat. Consequently, since the total amount of the animal's heat is derived under this condition from the chemical energy of its food, the former must constitute a direct index of the oxidative processes.

The unit generally employed in measuring the amount of heat

¹ The first calorimeter experiments upon animals were made by Lavoisier and Laplace in 1780 (Mém. de l'Acad. d. Sciences).

² Equally large masses of different bodies require different amounts of heat, that of water being nine times greater than that of iron.

evolved is the calorie, *i.e.*, the quantity of heat which is necessary to raise 1 kilogram of water 1°C . (from 15° to 16°C). We also speak at times of the small calorie which refers to the amount of heat which is required to raise 1 gram of water 1°C . Supposing, therefore, that the quantity of water in the calorimeter weighs 10 kilos and that the temperature rises 1°C . every half-hour, then the amount of heat liberated by the animal during this time amounts to 10 calories or to 480 calories in the course of a day. This calculation, however, can be correct only if the body-temperature of the animal has remained the same during this period, and if the metal of the calorimeter has not absorbed an undue amount of this heat. The latter factor cannot possibly interfere with this determination if the instrument is well

FIG. 528.—SCHEMATIC OUTLINE OF THE RESPIRATION CALORIMETER.

A, Dead air space between copper and zinc walls; B, dead air space between zinc wall and wooden wall; C, dead air space between inner and outer wooden walls. E, tube for food; S and H, inlet and outlet for water; V, air circulation. (Atwater and Benedict.)

protected against heat-loss, and if the experiment is continued for a relatively long period of time.

More recently, Atwater has made use of calorimeters large enough to accommodate human beings, so that the heat produced by them may be brought into relation with their respiratory interchange. The air within this chamber is kept at a constant temperature by a stream of water passed through it in a series of tubes. If the temperature of this water, as well as the volume of the through flow which is required to accomplish this end, is then ascertained, it is possible to obtain from these values the amount of heat liberated by the person. Besides, air is drawn out of this chamber by an engine, its volume being registered by a gas-meter. From time to time samples of this air are withdrawn for analysis which includes the determination of its carbon

dioxid content by means of baryta water and of its aqueous vapor by means of drying-tubes containing sulphuric acid. These values are then compared with the data derived from analyses of the air entering the calorimeter. These principles which have first been made use of by Pettenkofer, are also embodied in the *micro-calorimeter* of Hill.¹ This apparatus which is especially adapted for the detection of very small amounts of heat, consists of two thermos bottles in which the loss of heat is prevented by exhausting the air from the space between their outer walls. Each bottle is equipped with thermo-electric elements which are connected in turn with a galvanometer. Both are packed in sawdust. The organ to be experimented upon is then placed in one of these bottles, while the other is filled with water as a

FIG. 529.—DIAGRAM SHOWING CIRCULATION OF AIR THROUGH THE RESPIRATION CALORIMETER. (Atwater and Benedict.)

control. This apparatus is sensitized to detect one small calorie of heat per gram of tissue during a period of 10 hours.

Sources of Heat. Thermogenesis.—While there is always a small and variable amount of heat imparted to living beings from without, their principal source of heat lies in the chemical processes evoked within their different tissues and organs. Every contraction of muscle, every act of secretion, and even every nervous reaction gives rise to a small amount of heat, which together then form the total quantity of heat evolved by the animal. These cellular oxidations consist essentially of a union of oxygen with carbon and hydrogen to form carbon dioxid and water. In last analysis, therefore, the body-heat is derived from the food taken into the body. Other processes of disintegration, such as are effected by hydrolysis, also produce a certain

¹ Jour. of Physiol., xlv, 1918, 261, and *ibid.*, xlvi, 1913, 81; also: Williams, Jour. Biol. Chem., xii, 1912, 349.

amount of heat which, however, is never considerable. Inasmuch as the law of the conservation of energy is directly applicable to the animal body, these processes must serve to convert latent or potential energy into its kinetic form. Consequently, the ultimate source of heat is the potential energy of the food, and it matters little whether this material be slowly oxidized in the body or be burned up in a calorimeter. In both cases, complex substances are reduced into relatively simple bodies under an evolution of energy which manifests itself as mechanical energy, heat, and electricity. This combustion, however, remains incomplete at times, as is shown, for example, by the proteins which always leave a residue of urea, uric acid and other substances. Consequently, any calculation of the total heat-energy of a given foodstuff must take into account the energy of this possible residue. Carbohydrates and fats, on the other hand, are oxidized completely.

Body-temperature.—Since all the tissues of our body take part in these processes of oxidation, every cell in our body may be said to be a producer of heat. Admittedly, however, tissues differ very markedly in their activities, and hence, also in the quantity of heat evolved by them. The most important heat-generating organ is the skeletal musculature, because it is hardly ever at rest, and because more than one-half of the total weight of the soft parts of our body is made up of this type of tissue. Next in order are the glands. In either case, an active organ is always warmer than a resting organ or the body-fluids, and hence the heat must be transmitted from the former to the latter. In the nature of things, the chief and final heat absorbing agent is the blood which by virtue of its velocity quickly removes the superfluous heat from the seats of the oxidations, thereby tending to keep the temperature approximately uniform throughout. Later on, when the blood enters the more exposed portions of our body, it loses a part of its heat either by radiation or in the form of bound heat.

It is evident, therefore, that the blood and lymph form a medium into which the different tissues pour their heat and which by virtue of its motion tends to equalize the temperature of the different parts of the body, and also to bring the latter into proper heat-relation with the surrounding air. In accordance with their resistance to outside influences, animals may be divided into two classes, namely, into those which are and those which are not protected against a loss of heat. This functional difference brings it about that the former are capable of retaining a relatively constant temperature in spite of the fact that the outside temperature may vary considerably, while the latter are not and must, therefore, be subject to the fluctuations of the temperature of the medium in which they live. The first are designated as constant-temperated, homoiothermal or warm-blooded animals, and the second as inconstant-temperated, poikilothermal, or cold-blooded animals. But since the poikilothermal animals may be made to attain a body-temperature equalling and even surpassing that of the homoio-

thermal animals, the terms of cold-blooded and warm-blooded are not well chosen. This classification, therefore, rests upon their power of retaining a relatively constant body-temperature.

It should be noted especially that the temperature of the poikilothermal animals is invariably somewhat higher than that of the medium in which they live. This discrepancy cannot surprise us, because even an apparently perfectly inactive animal cannot suppress its metabolism entirely, and hence, since it must generate at least a slight amount of heat, its temperature must remain at least a degree or two above that of the surrounding medium. In other words, even cold-blooded animals store their heat in a certain measure, but this storage is never considerable, because they are relatively unprotected against heat-loss and secondly, because their metabolism per unit of weight is much lower than that of the warm-blooded animals. It should also be noted that the temperature of the warm-blooded animals is not absolutely uniform, because those leading a more active life, possess a higher body-temperature than those which do not. This becomes apparent immediately if the rectal temperature of the birds (41° to 44° C.) is compared with that of the mouse (41° C.), rabbit (39° C.), dog (38° to 39° C.), man (37° C.), and horse (36° C. to 37° C.).¹ With the exception of a few hibernating animals, which are homoiothermic in summer and poikilothermic in winter, the temperature of the warm-blooded animals must remain rather constant, otherwise certain conditions may arise which will make life impossible.² The vitality of cold-blooded animals, on the other hand, is not seriously impaired by such variations, as is evinced by the fact that the temperature of the frog may be reduced from 25° C. to 5° C. without producing other symptoms than a mere sluggishness of movement.

The Temperature of Different Regions of the Body.—It has been stated above that the different tissues of our body eliminate heat in amounts corresponding almost precisely with the intensity of their metabolism. The muscles come first, then the glands, and lastly the nervous and connective tissues. Furthermore, while the heat produced by them is directly transmitted from part to part, the chief and final absorbing medium is the blood, but since the latter cannot equalize conditions instantaneously, some internal parts must always be warmer than others. This is true, in particular, of the liver, because its blood-vessels are well protected against heat loss, and because its metabolism is never at a standstill. But, the blood also traverses certain regions which lie in immediate contact with the medium and which, therefore, are more directly exposed to the influence of the latter. Thus, it has been observed that the temperature of the skin in the vicinity of a blood-vessel is higher than that at some distance from it, and that the temperature of the blood of the carotid artery is

¹ Frothingham and Minot, *Am. Jour. of Physiol.*, xxx, 1912, 430.

² Simpson, *Proc. R. Soc. (Edinb.)* 1912, and *Proc. Soc. Exp. Biol. and Med.*, 1913.

higher than that of the external jugular vein. Very similar differences are displayed by the blood of the portal vein before and after meals, as well as by the blood of the vein draining a muscle when the latter is either allowed to rest or is made to contract. Even the mere raising of the arm above the head suffices to lower the temperature of the hand 0.2°C .

The average temperature of the blood traversing internal channels, is 39° to 40°C ., while that of the exposed parts may be only 28° to 35°C . Kunkel¹ gives the following values: Forehead 34.1°C ., cheeks 34.4°C ., tip of ear 28.8°C ., sternum 34.4°C ., and thigh 34.2°C . In man, the body-temperature is measured as a rule by placing the thermometer below the tongue, care being taken to keep the lips closed to prevent its cooling by the respiratory currents of air. In adults, it may also be measured in the axilla, and in children usually in the rectum. While the time during which the thermometer should be left *in situ*, varies with its sensitiveness, 2 to 3 minutes usually suffice for its indicator to reach its highest level. The average axillary temperature is 36.9°C ., the oral temperature 37.1°C ., and the rectal temperature 37.3°C .

Factors Varying the Body-temperature.—While it is our custom to adhere strictly to these average values, it should be remembered that certain minor fluctuations are not at all uncommon. In other words, even the homiothermal animals frequently show variations in their temperature which are brought about by such factors as age, sex, time of day, meals, exercise, season, climate and clothing. While these deviations rarely amount to more than a degree or two and are temporary in their nature, certain conditions may also arise at times which produce a much more intense and lasting difference. Quite aside from the ordinary febrile reactions, the outside temperature may be raised in such a measure, that, owing to a diminished loss of heat, the body-temperature quickly mounts to 40°C . and over. This change is usually associated with the symptoms characterizing fever and heat-stroke, *i.e.*, with an increase in the frequency of the heart and respiration (heat-polypnea), fatigue, headache and loss of consciousness. When the rectal temperature rises to 44°C ., death usually results within a very short time.

Hot moist air is far more oppressive and dangerous than hot dry air, owing to the inability of the body to rid itself of the superfluous heat by sweating. In other words, in the former instance ordinary radiation cannot be augmented so well by a loss of heat in the form of bound heat. In this regard, the cold-blooded terrestrial animals have the advantage, because they are able to burrow underground or to dive under water to increase their evaporation. Very similar conditions exist in the plants, because any rise in the external temperature increases their transpiration, thereby lowering their own temperature much below that of the atmosphere. This protects them against dry-

¹ Kunkel, *Zeitschr. für Biol.*, xxv, 1889, 69.

ing. In animals an extreme drop in their body-temperature may be produced by exposing them to cold air or water. Owing to the reduction in the warmth of the tissues then ensuing, the nerve centers soon lose their irritability, which condition in turn gives rise to paralyses of motion and sensation. While it is difficult to give a precise lower limit, recovery has been noted in persons whose body-temperature had been reduced to 24°C .

As far as the minor fluctuations are concerned, it should be noted first that the body-temperature of children is higher than that of adults, amounting to 37.8°C . at birth and to 36.8°C . shortly afterward. Within the succeeding 24 hours, however, the heat-regulatory mechanism becomes functional and the temperature rises to 37.5°C . Between puberty and the age of forty it remains at 37.1°C . A slow decline then sets in until about the seventieth year, when it again rises. The diurnal variations in the body-temperature are closely allied to the changes in the intensity of the metabolism, being lowest at about 5 o'clock in the morning and highest at about 6 or 7 o'clock in the evening. Besides, they may be greatly modified by the occupation of the individual. Thus, they are commonly reversed in persons who follow their vocation at night and sleep during the day. After meals the body-temperature is somewhat higher than normal, owing to the increased glandular activity and peristalsis, as well as to the heat liberated by the food. Iced drinks and cold food, on the other hand, abstract heat from the body and tend, therefore, to cause a slight reduction, if used in large amounts. An insufficient intake of food lowers the temperature because it tends to lessen metabolism. Any one of these changes, however, rarely amounts to more than 0.2 or 0.3°C . and does not last long.

It is a matter of common experience that muscular exercise affects the body-temperature in a very decisive manner. Thus, even such relatively slight efforts as are required to play a game of tennis, suffice to raise it a degree or two above normal, but inasmuch as this activity invariably increases the bloodflow, this superfluous amount of heat is soon dissipated. During the summer, the mean body-temperature exceeds the normal by as much as 0.5°C ., and even the ordinary changes in the outside temperature occurring in the course of a day, may vary the body-temperature by several tenths of a degree. Much more decisive changes follow the immersion of the body in warm or cold water.¹ Those mammals which at the approach of winter enter the state of hibernation, suffer a constant loss of heat until their temperature has reached a level only slightly above that of the surrounding atmosphere. Evidently, this effect depends in large part upon a lessened heat-production brought about by a reduction in their bodily activities. Upon awakening in the spring, their temperature frequently mounts very rapidly in complete correspondence with the rather sudden resumption of their active life. Drugs affect the

¹ Dill, *British Med. Jour.*, 1890.

body-temperature in different ways. Such agents as alcohol lower it, because they stimulate the circulation and dilate the peripheral blood-vessels. Both these changes, therefore, favor heat-dissipation. The anesthetics and narcotics also lower it, because they depress the oxidations and relax the blood-vessels. Strychnin, cocain and nicotin increase it.

The Regulation of the Body-temperature. Thermotaxis.—The mere fact that the homoiothermal animals are able to retain a rather uniform temperature in spite of their inconstant rate of heat-production and almost incessant variations in the surrounding medium, proves beyond a doubt that they must be in possession of a mechanism whereby their body-temperature is regulated. Clearly, a constant body-temperature can only be obtained if the dissipation and production of heat are accurately balanced, and hence, any change therein must show that one of these factors is more powerful than the other. Thus, a rise in the body-temperature may be due either to a greater heat-production or to a diminished dissipation, or both. Quite similarly, a lowering of the body-temperature may arise either in consequence of a lessened heat-production or an increased heat-dissipation, or both. In many cases, however, it is quite impossible to state definitely which of these two factors is at fault unless the fundamental cause of the variation is known. Thus, it is commonly held that fever is due to a greater production of heat, although it will be shown later on, that the heat-dissipating mechanism, consisting of the vasomotor apparatus and the sweat-glands, is also deranged at this time.

It will be seen, therefore, that living animals behave very differently from dead animals, because the latter absorb and lose heat somewhat in the manner of inorganic bodies. It is a matter of common observation that inanimate material may be artificially warmed and cooled in accordance with its thermotactic properties. The plants occupy an intermediate position, because they possess certain qualities which allow them in a slight measure to resist outside thermic influences.

Heat-production. Thermogenesis.—Heat is a form of energy. It is not matter, but merely a peculiar state of matter, because, in accordance with the undulatory theory, the heat of a body is due to an extremely rapid oscillation or vibration of its molecular constituents. Now, since heat-rays occur free in nature, it is only natural to suppose that animals must receive some of this energy in the form of ordinary radiations from the sun or from artificial media. The chief and ultimate source of heat, however, lies in the potential energy of the food and, in a slight measure, also in hydrolytic cleavage. In this connection attention should again be called to the fact that the thermogenic power of the tissues differs greatly in accordance with their physiological purpose as well as with the state of their activity. Now, since muscular exercise leads to the evolution of a large amount of heat, it

may justly be concluded that muscular rest must lessen its production, although it can never stop it altogether. For similar reasons it may be assumed that paralyzed muscle must liberate only a very slight amount of heat, a fact which fully accounts for the coldness of these parts as well as for the feeling of chilliness experienced by the paralytic person. It is true, however, that in these cases the circulatory system is by no means performing its function properly so that the factor just mentioned is usually augmented by a greater loss of heat. An experiment directly bearing upon this question, is the following: If a rabbit is curarized and is kept alive by artificial respiration, any alteration in the temperature of the atmosphere changes its body-temperature very markedly in the same direction. Since this agent paralyzes the motor plates of the muscles, it nullifies the action of the most efficient heat-producing organ of the body and permits the entire system to become more fully dominated by outside influences.

The beneficial effect of muscular activity is also betrayed by the phenomenon of shivering, an involuntary reaction following an undue drop in the body-temperature. The object of this quivering is to produce heat to counterbalance the loss. If this is not sufficient, this reflex reaction is augmented by voluntary muscular contractions and mechanical impacts, the purpose of which is to augment the circulation. The efficiency of this reflex mechanism is also betrayed by the changes resulting in the metabolism of the warm-blooded animals in consequence of variations in the temperature of the atmosphere. Thus, it is a well-known fact that low temperatures increase and high temperatures decrease the metabolism and hence, also the production of heat. During the cold seasons of the year we are much more active. We eat more and gain in weight perceptibly, because a certain proportion of the excess material is stored. In hot weather, on the other hand, we are slack and incline to rest and sleep to lessen the production of heat.

Cold and warm baths possess a similar influence, the immersion of the body in water of 32 to 34° C. for a minute or two sufficing to increase the output of carbon dioxid considerably. This change, however, appears only if the person is in tonus and does not counteract this reflex reaction by remaining passive and willfully relaxing his muscles. In the latter case, the carbon dioxid output would be decreased, causing the body-temperature to drop. Furthermore, this drop need not always become apparent immediately; in fact, since the cooled external parts must slowly replenish the heat which they have lost at the expense of the internal structures, from 15 to 20 minutes may elapse before it is experienced. As soon, however, as the subcutaneous parts have regained their heat, the rectal temperature returns rapidly to normal. This process of equalization may be greatly hastened by voluntary muscular contractions as well as by deep and superficial massage. Another means of varying the production of heat lies in the character of the food ingested. Thus, the

person who restricts his diet to carbohydrates in summer and to meat and fat in winter unconsciously proves that the heat of combustion of the former is low and that of the latter high. This fact is illustrated further by the differences in the character of the food of the inhabitants of the northern and southern countries, the oily and fatty food of the far north being relished mainly on account of its high heat value. The influence of muscular contraction is elucidated further by the fact that very high temperatures are frequently encountered in tetanus and the status epilepticus. In addition, MacCullum¹ states that high temperatures are always noted in dogs when suffering from spasms following parathyroidectomy. Moreover, since these convulsions may be stopped by the administration of calcium acetate, this salt likewise reduces their body-temperature. These and other phenomena which might still be mentioned, show very clearly that the production of heat is controlled by involuntary and voluntary impulses involving the different tissues, chiefly the muscles.

Heat-dissipation. Thermolysis.—An animal loses its heat in two ways, namely, by radiation or conduction from its skin and mucous surfaces, and in the form of bound or latent heat in its different fluid and semi-solid excreta. The channels which take part in this dissipation are the skin, pulmonary tract, alimentary canal and urinary passage. From the skin heat is lost by radiation, conduction and convection as well as in the form of bound heat in its secretions, the sweat and sebaceous material. The pulmonary passage transfers heat to the inspired air both directly as well as in the watery particles which are added to the expiratory air. The alimentary canal discharges a certain amount of heat in the feces and also imparts some of it to the food when taken into the mouth and stomach. Obviously, the temperature of the latter must be raised to that of the body. The urinary tract gives off a certain amount of latent heat in the urine.

Under ordinary conditions by far the greatest loss of heat occurs through the skin and its appendages. Furthermore, since the intensity of radiation depends upon the nature of the surface as well as upon the excess of temperature of the radiating surface over that of the surrounding medium, it will be evident that the uncovered areas of the skin must discharge a greater amount of heat than those protected by hairs or clothing. In addition, it is to be noted that the more vascular regions, such as the forehead, radiate more heat than the less vascular ones, such as the lobules of the ears or the tip of the nose. In either case, however, the loss of heat may be increased by moving about or by setting up currents in the surrounding air, because these procedures tend to augment the difference in the temperatures of the radiating surface and the absorbing medium.

In measuring the radiating heat we make use of an instrument which is constructed after the principle of the resistance thermometer and is known as the resistance radiometer or bolometer. It consists of

¹ Harvey Lectures, New York, 1903-09.

a grating of lead-paper or tinfoil which is arranged vertically in a closed box to protect it from air-currents. When the observation is to be made, the lid is removed from this box and the absorbing medium is adjusted at a definite distance from the skin. About 1725 calories are lost by the skin which corresponds to a loss of 69 per cent. of the total, provided the latter is estimated at 2500 calories for each 24 hours. The quantity of water evaporated from the skin may be estimated at 660 grm. in 24 hours. Since 0.582 calorie are needed to convert each gram of water into vapor, about 381 large calories are lost in this way. This corresponds to a loss of 15.3 per cent., making a total for the skin of about 85 per cent. of the entire heat dissipation.

The quantity of water evaporated from the pulmonary passage, is estimated at 400 grm. As each gram requires 0.582 calorie to convert it into vapor, the total loss effected through this channel amounts to about 232 calories, or 9.4 per cent. of the total. An additional 3.8 per cent. is apportioned to the inspiratory air to warm it to the temperature of the body. The remaining loss is covered by the warming of the food and drink upon its entrance into the body, and by the loss suffered upon its subsequent discharge from the body in the form of feces and urine. Estimated at 3 kilos with an initial average temperature of 12° C., about 60 calories are dissipated in this way. This indicates a loss of 2.8 per cent. of the total.

The many factors which may vary the intensity of heat-dissipation may conveniently be classified as involuntary and voluntary. Among the former are to be mentioned those reflexes which give rise to vasomotor, pilomotor and secretomotor reactions. It is a matter of every day experience that the skin and subcutaneous tissues pale under the influence of cold and flush under the influence of warmth. These changes indicate that cold constricts the cutaneous blood-vessels and drives the blood into the deeper parts of the body in an endeavor to diminish heat-dissipation. Warmth, on the other hand, relaxes these vessels and allows a more rapid escape of the body-heat. In the first case, thermolysis is also hindered in a varying measure by the secretion of the sebaceous glands, which the northern people carefully preserve and augment by anointing their body with oil and lard. Quite similarly, the aquatic animals are in possession of special glands which serve the purpose of covering their body with a fatty secretion. The function of the latter is to diminish friction and to protect them more thoroughly against an undue loss of heat. Upon this basis rests the practice of swimmers to anoint their skin with fatty substances. In the second case, the dissipation of heat may be greatly facilitated by moistening the body-surface with the secretion of the sweat-glands. In this way, a large part of the heat is lost in the form of latent or bound heat, and naturally, the higher the outside temperature and the dryer the air, the more rapid must be the evaporation and loss of heat. Contrariwise, a warm but humid atmosphere prevents the evaporation of the sweat and dissipation of heat. It is this secretomotor mechan-

ism which allows us to endure temperatures above that of the blood for days and even permits us to expose ourselves for a brief period of time to temperatures above that of boiling water.

While the amount of latent heat discharged by way of the respiratory tract, is inconsiderable in man, this channel-serves practically as the only means of thermolysis in many animals. This is especially true of those whose bodies are covered with thick fur which in itself hinders radiation. Thus, we note that the dog pants whenever a more copious loss of heat is made necessary. The respiratory air is then made to oscillate back and forth across the moistened mucous surfaces, and some bound heat is also lost in the fluid which dripples out of the corners of his mouth. At the approach of winter, these animals most generally acquire an even thicker coat of fur as well as more considerable amounts of subcutaneous fat. The value of the latter as a conserver of heat is well illustrated by the fact that water-fowls and especially those inhabiting very cold waters, are abundantly supplied with it. Moreover, since women are usually more copiously equipped with adipose tissue, they are in a better position to withstand cold than men. Heat may also be conserved by bringing the legs and arms in apposition with the trunk, because in this position a smaller area of the body is exposed to the surrounding medium. The opposite effect is produced by exposing the flanks more fully to the medium, a common practice among rabbits and dogs on warm summer days.

Among the voluntary factors controlling the loss of heat, might be mentioned the selecting and fitting out of the winter quarters of the hibernating animals, the building of nests, the adaptation of the dwellings of man to outside conditions, the wearing of clothing, and many others. The value of clothes lies in the fact that they hinder the free circulation of the air. Inasmuch as this medium is by no means a good conductor of heat, they retard the escape of radiant heat from the skin and become warm by absorption. This process is repeated at every successive layer of clothing, because each layer acts as a concentric air-jacket which tends to conserve the heat stored up in the water vapor right next to the skin. But the thickness of the clothing is not everything and attention must also be paid to its quality, inclusive of its porosity, weight, color and conducting power. Cotton and linen are good conductors and, therefore, allow the heat to escape more readily. Wool possesses the opposite qualities and is better adapted for cold weather. Besides, it is markedly hygroscopic and prevents a too rapid evaporation of the moisture and chilling of the body. The coarser the material, the greater its radiating power, and the cooler the clothing made from it. Furthermore, black clothing is warmer than white clothing, because it possesses a greater heat absorbing power. During sleep, when the metabolism and thermogenetic function of the tissues is at low ebb, extra covers are needed to prevent an undue loss of heat.

The Nervous Mechanism Regulating Thermotaxis.—Technically heat-production is designated as thermogenesis, heat-dissipation as thermolysis, and the relationship between these two factors as thermotaxis. The question concerning the part which the nervous system plays in thermotaxis, cannot be answered with certainty. We have previously seen that reflexes producing vasomotor and secretomotor changes, are constantly at play, and hence, it must be concluded that the central nervous system is closely concerned with heat-regulation. Thus, we find that the infant does not acquire this function until some time after birth, while other animals, such as the guinea-pig and chick, already possess it when they are born. In other words, thermotaxis follows a course parallel to that of the development of the nervous system, and this must necessarily be so, because the striated and smooth muscle tissues and sweat-glands must first obtain their innervation before they can be in a position to influence the body-temperature. Some doubt, however, still exists regarding the presence of separate heat-centers and heat-nerves. For all that matters, every motor nerve of skeletal muscle may really be regarded as a heat-nerve and every nucleus as a heat-center, because the impulses generated by them not only influence muscular activity but also their production of heat. Consequently, the condition existing here, is very similar to that previously observed in the case of the trophic nerves, when we came to the conclusion that the nutritive state of a tissue is dependent upon the ordinary motor impulses relegated to it, and not upon separate impulses of a purely trophic kind.

Many observers have found that injuries to various parts of the cerebral cortex, basal ganglia, and medulla give rise to changes in the body-temperature. Thus Krehl, Ott,¹ Reichert,² and others, have noted that the transverse division of the corpora striata invariably produces a pronounced rise in the body-temperature (110° F.) and death. Other *heat-accelerator* centers have been localized in the tuber cinereum, cruciate sulcus, and the juncture of the suprasylvian and postsylvian fissures. *Heat-inhibitory centers* have been localized in the medulla and region of the pons. The evidence at our disposal, however, is too meager to warrant definite conclusions, because many errors have undoubtedly crept in on account of the character of the methods which must necessarily be practised in experiments of this kind. The latter consist in the destruction of parts, transection of paths, cauterization and puncture. Secondly, it is very possible that the results of these procedures are dependent in a large measure upon disturbances of the vasomotor (tuber cinereum) and musculomotor mechanisms (medulla), and not upon a derangement of the function of true heat-centers.

¹ Jour. Nerv. and Mental Dis., 1884.

² Univ. Penna. Med. Magazine, 1894; also White, Jour. of Physiol., xii, 1891, 233; Tangl, Pflüger's Archiv, 1895; and Sachs and Green, Am. Jour. of Physiol., xlii, 1917, 603.

The Total Quantity of Heat.—The total quantity of heat liberated by an animal is ascertained (a) by determining the heat values of the different foodstuffs ingested by the method of direct oxidation, and (b) by measuring the heat evolved by it with the help of the water or air-calorimeter. But whether reduced into its constituents in a bomb-calorimeter or more slowly burned in the body, the food yields the same amount of heat, provided it is fully consumed and is not allowed to discharge its energy as work. A plant exposed to sunlight, combines carbon dioxid and water into sugar, while oxygen is given off and heat is absorbed. Now, if 1 gm. of sugar is placed in a steel receptacle (Berthelot) into which oxygen is passed under a pressure of 450 lbs. to the square inch, the combustion of this substance may be incited by an electric spark.¹ It will then be found to have yielded carbon dioxid and water and an amount of heat equal to that absorbed. The latter is determined by immersing the steel receptacle in a liter of water. On determining the temperature of this water by means of a thermometer, it will be noted that it has risen 3.755° C. during this combustion. It may then be said that 1 gm. of sugar furnishes 3.755 calories of heat, because 1 calorie is the quantity of heat required to raise 1 kilogram (1 liter) of water 1° C. This method of absolute reduction in the bomb-calorimeter has also been applied to a large number of other food substances with the following results:

Animal fat.....	9.500 calories	Casein.....	5.867 calories
Butter.....	9.231 calories	Egg albumin....	5.735 calories
Olive oil.....	9.489 calories	Beef.....	5.640 calories
Glycerin.....	4.317 calories	Veal.....	5.662 calories
Elastin.....	5.961 calories	Albumins.....	5.711 calories

The different carbohydrates have yielded the following heat values:

Dextrose.....	3.742	Maltose.....	3.949
Levulose.....	3.755	Starch.....	4.182
Galactose.....	3.721	Dextrin.....	4.112
Cane sugar.....	3.955	Cellulose.....	4.185
Milk sugar.....	3.951		

From these figures Rubner² has deduced the following "standard" values:

1 gram of protein.....	4.1 calories
1 gram of carbohydrate.....	4.1 calories
1 gram of fat.....	9.3 calories

These values, however, are physical values and represent the heat evolved by them when completely oxidized to carbon dioxid and water. In the animal body these substances are not always thoroughly utilized and hence, their nutritive value may not correspond precisely with these figures. This is true in particular of the proteins, because in the bomb-calorimeter the nitrogen of these substances is converted into nitric acid, while in the body they are oxidized to urea. Conse-

¹ Schlossmann, *Zeitschr. für phys. Chemie*, xxxvii, 1903, 324.

² *Zeitschr. für Biol.*, xlii, 1901, 261; also: Atwater, *Am. Jour. of Physiol.*, x, 1904, 30.

quently, the heat liberated by the proteins in the body is less than that obtained when they are burned in the bomb-calorimeter. The carbohydrates and fats, on the other hand, are reduced to carbon dioxid and water and produce, therefore, practically as much heat in the body as when oxidized in the bomb. In the latter case, the discrepancy amounts to only 3 per cent. and is dependent upon the fact that some portions of these substances escape unutilized into the feces. In the case of the proteins, on the other hand, this loss amounts to 20 or 25 per cent. which is caused in part by their entrance into the feces (1.0 to 1.3 per cent.) and in part by their incomplete reduction into urea. But as this compound may be further split up in the bomb to carbon dioxid and water under liberation of heat, it becomes necessary to deduct this amount of heat from that obtained during their physical combustion. According to Rubner, 1 grm. of urea yields 2.523 calories; moreover, since this amount of urea requires the oxidation of 3 grm. of protein, the amount of heat to be deducted from the heat-value of protein substance is 0.841 calorie. This loss, together with that incurred by the escape of protein into the feces, reduces the physiologic heat-value of this foodstuff to about 4.124 calories.¹

The experiments of Voit and Rubner upon dogs have shown a very close correspondence between the heat values of the different foodstuffs calculated in the above manner and those obtained in the calorimeter. These results are fully upheld by the determinations of the heat-production in normal men under different conditions of life. Thus, it has been found that the basal value in an adult weighing 70 kilos (156 pounds), is 70 calories in 1 hour or 1.680 calories in 24 hours. This term of *basal heat-production*, however, signifies that the person has received no nourishment during the preceding 15 hours and has continued to rest in bed after a night of sleep. If any food has been taken during this period, about 168 calories should be added to this total, which makes 1.848 calories in all. Exercise increases this value very materially, and naturally, this increase must be compensated for by a larger intake of food. According to the experiments of Atwater and Benedict,² the efforts connected with arising and sitting in a chair increases the basal heat-production by 8 per cent. and the ordinary movements performed by us in the course of a day, by 20 per cent., thus:

Night.....	616 calories
Day.....	1.552 calories
<hr/>	
Total.....	2.168 calories

A man of medium weight, leading a sedentary life, requires 320 calories in addition to these 2.168, or 2.500 calories in all, in order to supply him

¹ Rubner, *Die Gesetze des Energieverbrauchs*, 1902, also: *Calorim. Methodik*, Marburg, 1891.

² *Ergebn. der Physiol.*, iii, 1904.

with sufficient fuel to carry on even the most moderate muscular activity.¹ Beyond this *ordinary heat-production*, the amount of fuel needed by a person is in agreement with the character of the exercise.² Farmers require on an average 3500 calories and six-day bicycle riders 10,000 calories per day. Boys, on the other hand, need only about 1500 calories, and babies 100 calories for each kilogram of body weight.

The Effect of Varnishing the Skin and Other Procedures.—The larger the surface of the body exposed to the cooler medium, the greater must be the loss of heat. Consequently, since a small animal presents a proportionately larger surface to the surroundings in relation to its mass than a large animal, its loss of heat must exceed that of the latter. Obviously, this more considerable thermolysis must be accurately balanced by a greater thermogenesis, and hence, the smaller animal must possess a more intense metabolism. This is evinced by its more rapid respiratory and cardiac rates.

While warm-blooded animals may survive a brief exposure to an outside temperature of from 100° to 132° C., owing to the profuse loss of latent heat then ensuing, cold-blooded animals are usually killed at about 40° C., because their musculature enters at this temperature the state of rigor caloris. Insects commonly withstand a temperature of 64° C. Even the ordinary temperature of a beehive varies between 30° and 40° C. which represents stagnated heat produced by the bees themselves. Plants wither at a temperature of 52° C. If left to themselves, warm-blooded animals usually do not survive when their body-temperature has been reduced to 20° C., but if artificial respiration and warmth are applied to them, they may recover from a temperature even lower than the one just given. Cold-blooded animals are able to withstand 1° C. and may even be partially frozen.³

The *hibernating animals* show signs of depression when their temperature falls below 28° C. At 18° C. they exhibit a decided drowsiness, at 6° C. semi-sleep and at 1.6° C. deepsleep.⁴ At this time, the heart beats only 8 to 10 times in a minute, while the respiratory movements cease altogether. The very small amount of oxygen which they now require is obtained by means of the volumetric changes which the heart undergoes during its cycle. On systole this organ becomes smaller, causing a slight amount of air to flow into the lungs, while on diastole, it becomes larger and forces an equal amount of air outward. This constitutes the so-called *cardio-pneumatic phenomenon*. When the hibernating animal awakes, its body-temperature may rise as much as 20° C. in the course of two hours.⁵

A rise in temperature may also result directly *after death*. Obviously, this effect must be produced by a continued heat-production and a diminished heat-dissipation, establishing a balance in favor of the former process. Thus, it may happen that the sudden cessation of the circulation prevents the escape of heat from the still active tissues. A most favorable condition of this kind is created when the body-temperature has been high beforehand, so that the interruption of heat-dissipation may allow an excessive stagnation of heat in the highly active tissues. Muscular spasms at the time of death augment this effect. Heat is also produced during the fixation of the muscles coincident with the onset of rigor mortis.

Covering the skin with a layer of varnish or paraffin has the same effect as cooling, because an animal so treated loses heat very rapidly, owing to the dilated condition

¹ Lusk, Science of Nutrition, W. B. Saunders and Co., 1909.

² Rumf, Pflüger's Archiv, xxxiii, 1884, 538, and Knoll, Archiv für Exp. Path. und Pharm, xxxvi, 1895, 305.

³ Müller-Erbach., Zoolog. Anz., 1891.

⁴ Merzbacher, Ergebn. der Physiol., iii, 1904, 14.

⁵ Pembrey, Jour. of Physiol., xxix, 1903, 195.

of its cutaneous blood-vessels.¹ If placed in a warm chamber or covered with straw or blankets, it invariably survives the critical period directly after the application of the varnish, because later on the hairs grow out sufficiently to disengage the varnish from the skin, allowing the latter at least partially to protect itself against this enforced loss of heat. The view that this procedure prevents the elimination of toxic substances through the skin, has not found experimental substantiation. The administration of *nervous depressants* most generally evokes a loss of heat against which the patient must be carefully guarded. Thus, extra blankets are to be placed upon a person who has been given chloral.

Hyperthermy and Hypothermy.—In addition to the variations in the body-temperature noted in the course of the previous discussion, brief reference should also be made at this time to the hyperthermy commonly following the entrance into the body of pathogenic bacteria and toxic substances, such as the derivatives of fermentative processes. This condition which is usually designated as fever, is represented by a complex of symptoms of which a decided and rather lasting elevation of the body-temperature is the most characteristic. Rises to 38° or 39° C. are usually spoken of as "low fever" or pyrexia, and rises to 41° C. as "high fever" or hyperpyrexia. Among the other readily recognizable signs are thirst, painful sensations, weakness, apathy, nausea, vomiting, alterations in the quantity and quality of the various secretions and excretions of the body, and such other changes as may be more specifically related to the infection. Fever may begin gradually, and more abruptly with a chill; it may be constant, remittent and intermittent; it may last a variable period of time and disappear either gradually or rather suddenly. In every case, however, it represents a physiological attempt on the part of the body to correct a disturbance of function, and hence, it is quite proper to refer to it as a reaction.

Fever or pyrexia may be due either to an increased production or to a diminished dissipation of heat, or both. Evidently, any disproportionality between these two factors which leaves a positive balance for heat, must bring about an elevation of the body-temperature. Concerning the first factor, we have the positive statements of Krauss,² Nebelthau,³ May,⁴ Staehelm,⁵ and others that thermogenesis is increased during fever, the difference amounting to as much as 25 to 50 per cent. Direct calorimetric determinations have also proved that the loss of heat is increased during fever, but in comparison with the enormous production of heat, the dissipation is undoubtedly diminished. In other words, the heat is stagnated, as is evinced by the livid, blue and cold character of the skin following the contraction of the cutaneous blood-vessels and the cessation of evaporation from the skin. When these changes first occur, a sensation of cold is experienced which causes the patient to draw his body into as small a mass as possible and to cover himself thickly with blankets. The quivering

¹ Krieger, *Zeitschr. für Biol.*, 1869; also Babak, *Pflüger's Archiv*, cviii, 1905, 389.

² *Zeitschr. für klin. Med.*, xviii, 1890, 91.

³ *Zeitschr. für Biol.*, xxxi, 1894, 293.

⁴ *Ibid.*, xxx, 1893.

⁵ *Zeitschr. für klin. Med.*, lxvi, 1904, 77.

of the muscles and goose-flesh appearing at this time greatly aid in sending the body-temperature upward. The height of the fever having been attained, heat-dissipation more nearly balances heat-production,¹ but is still inadequate to allow the abnormally large amounts of heat to escape. During the last stages of fever, the production of heat is diminished, while the dissipation of heat gradually increases, owing to the reestablishment of a proper control over the capillaries of the skin and the reappearance of the sweat.

The underlying causes of fever having been established, the question may now be asked how these changes are brought about. The two most acceptable explanations are contained in the so-called neurogenic and toxogenic theories of fever. The former has been put forth by Liebermeister² and holds that the heat centers regulating the body-temperature are raised to a higher pitch during fever, simulating our means of adjusting the regulator of a thermostat in such a way that the latter may yield a temperature of 40° C. instead of 35° C. In accomplishing this end, the heat centers make use chiefly of the vasomotor and secretomotor mechanisms. In this restricted form this theory seems to have little in its favor, but naturally, this statement does not imply that the ordinary reflexes are excluded as adjunct causative factors in the production of this form of hyperthermy. In fact, the evidence is against such a view, because the brief febrile reactions following the passage of biliary or renal calculi, catheterization, and various operative procedures, are undoubtedly produced by a diminished loss of heat incited by the reflex constriction of the cutaneous blood-vessels. Hirsch, Müller and Rolly³ have put forward the view that fever results in consequence of a derangement of the metabolic condition of the tissue cells by poisonous substances. This explanation has much in its favor, and is well adapted to those febrile reactions which follow upon the entrance of pathogenic bacteria into the system. The implication is that the cells respond to these substances with an increased activity,⁴ thereby endeavoring to accomplish some beneficial effect. Since the intake of food is much diminished at this time, this metabolic augmentation is had mainly at the expense of the organized constituents of the body.

The preceding conclusion is upheld by the fact that fever greatly affects the metabolism, but probably not so much its intensity as the manner in which it involves the different foodstuffs. The deduction that it is not merely a matter of intensity of oxidation, is upheld by the fact that the amount of the oxidation products derived from febrile combustions is very small, as well as by the fact that the respiratory quotient remains practically unchanged.⁵ It appears, therefore, that these

¹ Krehl, *Zeitschr. für allg. Physiol.*, i, 1902, 29.

² *Pathologie des Fiebers*, 1875.

³ *Deutsch. Archiv für klin. Med.*, lxxv, 1903, 265.

⁴ Rolly and Meltzer, *ibid.*, xciv, 1908, 335.

⁵ Senator and Richter, *Zeitschr. für klin. Med.*, lix, 1904, 16.

disturbances do not lie in the oxidation of the non-nitrogenous substances, but rather in that of the proteins. Furthermore, since the intake of food is greatly diminished in fever, the oxidations must go on chiefly at the expense of the protein of the tissues. This is proved by the fact that the total excretion of nitrogen is increased, at least, in proportion to the amount of protein ingested, and reaches its highest value directly after the crisis and during the period of defervescence. It appears, therefore, that the products of the bacteria give rise to some derangement of the protoplasm of the cells, in consequence of which they are rendered especially vulnerable to the hydrolyzing and oxidizing agents which are always present in the tissues. The constant drain upon the store of the tissue-proteins then ensuing, cannot be made good by a corresponding intake nor are the cells able to protect their proteins sufficiently by means of carbohydrates and fats. Consequently, this tearing down process must continue and give rise eventually to an excessive production of heat which is not compensated for by an equally intense dissipation. In other words, fever is the result and not the cause of this disorder in the metabolism of the tissues.

The common view is that fever is a pathological process and must be combated, because the body cannot long withstand a temperature of from 44° to 45° C. But since fever is merely one of the expressions of a cellular reaction instituted in consequence of pathogenic influences, its removal by cold baths and drugs cannot give permanent nor beneficial results. Whether fever as such possesses a favorable influence upon the body and actually helps in combating the pathogenic process is a much debated question. Bacteriologists, however, claim that it serves as a protective mechanism, because many bacteria are killed at a temperature slightly above that of the body. This is true of the streptococcus of erysipelas which does not develop at 39° to 40° C., as well as of the bacillus of anthrax which, when kept at 42° C., is greatly attenuated. Even the temperature range of the bacillus of diphtheria and of the pneumococcus is limited. It has also been suggested that a high body-temperature may be required for a copious formation of immune bodies which would then remove the cause of the abnormal protein-metabolism by antagonizing the agent of the infection.

PART IX

REPRODUCTION

SECTION XXX

THE REPRODUCTIVE ORGANS

CHAPTER XCIII

GROWTH, REGENERATION AND REPRODUCTION

Direct Cell-division or Amitosis.—The preceding pages have been devoted very largely to a discussion of the processes of life as we find them in the adult animal. Looked at in a very general way, these processes present themselves as phenomena of activity and growth. Both of these take place at the expense of the inorganic and organic material of the surrounding medium, and are the direct outcome of stimulations. Consequently, life is not spontaneous, but consists merely of responses to external and internal impressions. Sooner or later, however, these reactions cease and retrogression gains the upper hand. Henceforth dissimilation continues uninterruptedly until the complex animal machine has ceased to exist as a living entity. Thus, death is merely a phenomenon of nature, brought about by a serious derangement of the processes upon which life is based. It is the climax of all physiological activities.

Since the chief consequence of death is the extinction of the individual, not only the existence of a certain species but also that of all animal life would be endangered. In order to prevent such an outcome, nature has provided a process of rejuvenation by means of which new living entities may be brought into existence to take the places of those used up. This constitutes the process of reproduction. Fundamentally considered, the aspect of reproduction is the same as that of growth, because it strives to accomplish a multiplication of the living substance at the expense of the surrounding material. In the case of growth, however, the new substance is affixed to the same entity, while in the case of reproduction, it is moulded into an entity separate from the original.

Attention has previously been called to the fact that the size of any given unit of living matter is limited, because it is held together

by nothing more than the ordinary force of cohesion. Hence, if its mass becomes too large, this force, amplified by adhesion, is no longer sufficient to act throughout its substance, in spite of the fact that the proportion of its surface to its mass becomes less as its size increases. Moreover, since the processes of life are controlled by the nuclear material and not by the cytoplasm, the mass of the latter must be restricted, otherwise the nucleus cannot make its influence felt throughout the cell. It is for this reason that those cells which must of necessity attain a large size, such as the leukocytes and giant cells, invariably embrace several isolated nuclei. To begin with, of course, the growth of these simple protoplasmic units depends upon the fact that their acquisition of new material exceeds the destruction. Eventually, however, when a limit in their size has been reached, their assimilative power is gradually diminished. Even a division of their mass may then result, but only if it is also in possession of a sufficient amount of nuclear substance. When the latter is removed completely, the cytoplasm cannot continue to exist for any length of time, because it then lacks its "trophic" factor.

Contrary to growth, therefore, the process of reproduction depends upon the formation of daughter-cells by the division of the mother-cell; but it will be seen that these occurrences are not independent of one another, because without activity and growth there can be no reproduction. The manner in which this rejuvenation of living matter is accomplished differs greatly in different animals. The simplest procedure prevails in the unicellular organisms, because these entities multiply by the asexual process of *simple division or amitosis*. The mother-cell splits into two parts, each of which is equipped with a certain amount of nuclear substance. In accordance with Remak (1858), cell-division begins with a splitting of the nucleolus which is then followed by a constriction and division of the nucleus, cell-body and enveloping membrane. The daughter-cell so formed grows and gradually acquires the characteristics of the mother-cell, but only if it is subjected to identical conditions. If not, its molecular and general morphological character may be altered in such a manner that it may give rise to an entirely new species.

This amitotic manner of reproduction frequently gives rise to a perfectly amazing multiplication. Thus, it has been stated that a paramecium, if it were plentifully supplied with food and protected against injurious influences, would be able to form in the course of a year a mass of living matter as large as the earth. If nothing more, this computation gives us an idea regarding the perfectly phenomenal possibilities of this process. But, it is also true that amitosis cannot continue for an indefinite period of time and certainly not if the organisms are forced to exist under unfavorable circumstances. It seems that they then lose their vigor and become non-resistant so that they are more easily affected by outside influences. Under these conditions, a type of reproduction is frequently brought into play which is called

conjugation and which undoubtedly is a prototype of the interaction of the germ-cells of the multicellular forms. Conjugation is essentially a union of the nuclei of the conjugating cells, although in unicellular plants the cell-bodies are fused as well, while in the infusoria this union is only temporary. Maupas¹ believes that this process invariably follows a long period of multiplication by cell-division and may be compared to the attainment of sexual maturity of the higher animals. According to Bütschli, its purpose is to prevent senile retrogressive changes and to instil new vigor into the descendents.

In the infusoria, Wilson² recognizes the following changes: To begin with, each cell possesses two kinds of nuclei, namely, a large macronucleus and one or several micronuclei. As soon as the cells have become applied, the former degenerates and disappears. In consummating this process, the micronucleus divides twice to form four spindle-shaped bodies. While three of these degenerate, the fourth splits into smaller masses. These micronuclei are then exchanged, one from *A* passing into *B* and one from *B* into *A*. Very soon after these cells have again separated each pair of nuclear masses unite into one. This single micronucleus then divides three times to form eight; while the cell meanwhile splits into four parts, two nuclei being apportioned to each daughter-cell. One of the latter enlarges to form the macronucleus, while the other continues as the micronucleus.

Indirect Cell-division or Mitosis.—By far the greatest number of animal and vegetable cells multiply by the process of mitosis or karyokinesis, which differs from amitosis chiefly in the fact that the nucleus undergoes a number of very characteristic changes. In order to be able to follow these more conveniently, they may be divided into the following phases:

- (a) Prophases, during which the division is initiated.
- (b) Metaphase, during which the nucleus undergoes its most important change.
- (c) Anaphases, during which the nuclear material is arranged in a peculiar manner, preparatory to the
- (d) Telophases, during which the active cell divides, giving rise to the daughter-cells.

During the *prophase* the chromatine substance of the nucleus acquires a greater power of staining, loses its net-like character and is eventually resolved into a definite number of separate bodies possessing intense staining qualities. These so-called chromosomes are generally rod-shaped, straight or curved, but may also be spherical, ovoidal or ring-like. They arise in consequence of the transverse division of the spireme-thread into which the nuclear substance first resolves itself. In the place previously occupied by the nucleus, the cytoplasm assumes a radiate appearance, giving rise to a star or aster. In the center of each aster lies a centrosome, while in between them is a spindle of fine fibers, known as the achromatic spindle. The chromosomes arrange themselves in a plane at the equator of the spindle.

The *metaphase* is characterized by a lengthwise splitting of the chromosomes into equal halves, thus initiating the actual division of the cell. During the *anaphase* these daughter-chromosomes move toward the opposite poles of the spindle

¹ Arch. de Zoologie, Sec. II, vii, 1889.

² The Cell in Development and Inheritance, Macmillan, 1919.

and collect here in groups, finally evoking the formation of a daughter-nucleus. As they diverge, the zone between them shows a bundle of achromatic connecting fibers which are not identical with the fibers of the original spindle. Later on in

FIG. 530.—THE PROPHASES OF MITOSIS (HETEROTYPICAL FORM) IN PRIMARY SPERMATOCYTES OF SALAMANDRA.

A, Early segmented spireme; two centrosomes outside the nucleus in the remains of the attraction-sphere. B, longitudinal splitting of the spireme, appearance of the astral rays, disintegration of the sphere. C, early amphiaser and central spindle. D, chromosomes in the form of rings, nuclear membrane disappeared, amphiaser enlarging, mantle-fibers developing. (Meves.)

the course of the anaphase and during the *telophase*, the entire cell splits into two portions, each of the daughter-cells receiving a group of chromosomes, half of the spindle and connecting fibers and an aster with its centrosome. Meanwhile, the nucleus of the daughter-cell has been reconstructed.

It has been shown that the number of chromatic loops differs greatly in different animals but is constant in the same species. Man has sixteen chromosomes in the nucleus of his somatic cells, while the mouse and salamander have twenty-four, those of *Ascaris* two or four, and those of the crustacean *Artemia* one hundred and sixty-eight. It appears, therefore, that mitosis effects a meristic division of

FIG. 531.—METAPHASE AND ANAPHASES OF MITOSIS IN CELLS (SPERMATOCYTES) OF THE SALAMANDER.

E, Metaphase. The continuous central spindle-fibers pass from pole to pole of the spindle. Outside them the thin layer of contractile mantle-fibers attached to the divided chromosomes of which only two are shown. Centrosomes and asters. *F*, Transverse section through the mitotic figure showing the ring of chromosomes surrounding the central spindle, the cut fibers of the latter appearing as dots. *G*, Anaphase; divergence of the daughter-chromosomes, exposing the central spindle as the interzonal fibers; contractile fibers (principal cones of Van Beneden) clearly shown. *H*, Later anaphase (dyaster of Flemming); the central spindle fully exposed to view; mantle-fibers attached to the chromosomes. Immediately afterward the cell divides. (*Drüner*.)

the chromatin of the mother-cell, so that the daughter-cells may be equally provided with this material. Amitosis, on the other hand, presents itself rather as a division of mass.

Regeneration.—Besides growth, an organism has two duties to perform, namely, to reproduce the cells which have been used up in its processes of life, and secondly, to reproduce its like in the form of

a new living entity. The former process or regeneration may be participated in by practically any one of the constituents of its several tissues, while the latter or reproduction, is effected by a special group of cells. In fact, the propagation of the species is so important a function that it is generally mediated by a set of specialized cells constituting the organs of reproduction. Thus, the cells of a multicellular organism really arrange themselves into two groups, namely, into those mediating its ordinary processes of life and those concerned with the generation of a new organism. Weissman applies to the former the term of somatic cells, and to the latter, the term of germ-cells. As far as the actual life of the animal is concerned, these reproductive units are of relatively slight importance and are brought into play only when new entities are to be formed. But since even somatic cells are able to reproduce their like, this distinction is not absolute, but merely serves to indicate a physiological division of labor of the cells of the metazoan.

The life of the organism as a whole is limited and so is that of the numberless constituents of its different tissues. Cells are constantly being destroyed, more so in some tissues than in others, and their places are taken by new units. This implies that even the ordinary tissue-cells must possess the power of reproducing their like. Thus, we have previously noted that the red blood corpuscles disintegrate while they traverse the circulatory system, and are constantly being replaced by new cells derived from the red marrow of the bones. A similar regeneration takes place in the outermost layer of the skin where the squamous epithelium is worn away and is restored by newly formed cells of the deeper Malpighian layer. When exercised, the skeletal muscle acquires new cells, and so does the uterus after its reception of the impregnated ovum. The periosteal cells proliferate when the adjoining bone is broken (callus), giving rise to numberless bone-corpuscles, many of which are again absorbed later on. Under ordinary circumstances, however, some of the adult tissue-cells are quite unable to reproduce their like, which implies that other cells must step in to consummate this process. Thus, a wound in a muscle is usually closed by a proliferation of its connective tissue elements and not by a multiplication of its muscle cells. This gives rise to the formation of scar-tissue. Furthermore, these processes of regeneration are invariably retarded after middle life and may in fact be abolished altogether. As an instance of this abolition might be mentioned the abortive proliferation of the cells of the periosteum, causing a permanent separation of the ends of the fractured bone.

In general, it may be said that the more highly organized tissues are regenerated with greater difficulty than those of a more elementary kind. This is especially true of the master tissue of our body, at least insofar as the cell-bodies of the different neurons are concerned, because defects of the central gray matter are always repaired with

extreme tardiness. Harrison,¹ however, has proved that nerve cells may also be grown outside the body in suitable culture media. When clotted lymph is used, the cell-body grows and sends out its oxone and dendrites which may be traced far into the surrounding medium. This observation also proves that nerve fibers are the outgrowths of the hyaline protoplasm of the nerve cells which at this stage of development is actively ameboid. These long drawn out pseudopodia eventually become the organized fiber processes. Consequently, the central complexes of ganglion cells must exert a commanding influence upon the development of the fiber paths. This view finds substantiation in the fact that the transplanted limbs of the embryos of the toad and frog eventually acquire a normally arranged system of nerves.² No matter where the new limb is united with the body, these nerves show a perfectly normal distribution in relation to those of the host. Thus, a limb implanted in the region of the head, invariably acquires nervous outgrowths which are derived in regular order from the facial nerve or some other nerve, if closer to the graft.

In this category also belong the morphological and embryological experiments of Pflüger, Roux, Born, and others, purposing to test the regenerative powers of animals when injured during their period of development or when the organic constituents of the egg itself are either removed or transplanted from one animal to another. One of the most interesting discoveries was made by Born³ in 1894. While performing certain experiments pertaining to the reformation of lost parts of the embryo of the frog, he found that pieces which had first been absolutely separated from the main mass, might again be made to unite with it by simply holding them against it for a few hours. This preliminary fact having been established, he then succeeded in uniting these pieces in all possible ways, producing even monsters with two tails or two heads or a head in the place where the tail ought to be. Even pieces from different animals could be used in the production of these odd forms. With the help of the Zeiss binocular dissecting microscope and delicate instruments, Spemann⁴ was able to perform transplantations of much greater delicacy than those just related. These included the removal of certain areas of the epidermis or of the Gasserian ganglion and their implantation in some other part of the body; the removal and reversal of the auditory vesicle, as well as the interchange of the right and left ears. By the same means Lewis⁵ proved later on that the epidermis of any part of the body may be brought into contact with the optic vesicle at the proper stage of development and give rise to a crystalline lens.

¹ Proc. Soc. for Exp. Biolog. and Med., 1907.

² Held, *Verhandl. der anat. Gesellsch.*, Rostock, 1906, and Harrison, *Jour. of Exp. Zoology*, iv, 1907.

³ *Archiv für Entwicklungsmechanik*, iv, 1896-1897; also Brans, *Propfung bei Tieren*, *Verhandl. des naturhist. med. Vereins*, Heidelberg, iii.

⁴ *Verhandl. der deutsch. zoolog. Gesellsch.*, 1906.

⁵ *Am. Jour. of Anat.*, iii, 1904, and *Jour. of Exp. Zoology*, ii, 1905.

This list of regenerative possibilities, however, need not remain confined to the developing animal, but may also be extended to adult forms, because while the growth of the latter is greatly diminished, their power of reforming injured tissues is by no means lost. It is true, however, that their property of regeneration is rather dormant at this time, in consequence of certain inhibitory influences, but may be awakened temporarily by stimulation. Thus, it is a well-known fact that the adult starfish is capable of reforming a lost arm, and that a worm cut into is able to develop from the posterior extremity of its anterior segment a new tail, and from the anterior end of its posterior segment a new head.¹ In fact, even the severed arm of the starfish may eventually give rise to a complete animal, while artificial mouths surrounded by tentacles may be produced in sea-anemones by simply incising their body-wall and keeping the wound open. Of even greater interest are those experiments which show that parts of different animals may be united to form a single new one.² In this way, compound worms have been formed which lived for many months, and Harrison has even succeeded in uniting the anterior half of *Rana virescens* with the posterior half of *Rana palustris* (parabiosis). Although both parts retained their special characteristics, this compound frog gave rise to young. Most remarkable changes may also be effected in plants. Thus, it is a well-known fact that a whole plant may be produced from the cuttings of its branches and roots, and even from its leaves. In this category also belong the transplantations practised to enrich the flower and fruit bearing qualities of certain plants and trees. With regard to the growth of malignant tumors, it might be mentioned that connective tissues may readily be grown outside the body and that this growth may be greatly accelerated by extracts of tissues, particularly of embryos, spleen and malignant tumors.³ Tissues may also be kept at a low temperature without apparently losing their power of regeneration. Thus, skin may be kept for 2 to 6 weeks in cold storage and be grafted successfully at the end of this period.

Reproduction.—These examples, no doubt, suffice to show that regeneration is really a form of reproduction; but a reproduction of a local or restricted kind which does not pass beyond the reformation of the individual tissues. Thus, while a newt may reproduce an amputated toe, the newt itself is left in its original condition. Its cells are gradually used up until its existence as a living entity ceases altogether. But this natural limitation of life is prevented from

¹ Joest, *Transplantationsvers. an Regenwürmern*, Ber. Gesellsch. der Naturw., Marburg, 1895; also Morgan, *the Physiology of Regeneration*, Jour. Exp. Zoology, iii, 1906, or "Experimental Zoology," New York, 1907.

² The earliest experiments in grafting were performed upon hydra by Trembley (*Mém. pour servir à l'histoire d'un genre de polypes d'eau douce*, Leide, 1774). Later on Hunter and Durhamel grafted the spur of a cock to the comb where it continued to grow.

³ Carrel, Jour. Exp. Med., xiv, 1911, 571, and xvi, 1912, 165.

terminating the existence of the species by a process of regeneration or reproduction in mass. A special group of organs is set aside for the formation of what might be termed in brief the germ-plasm, a specialized substance which is capable not only of reforming a particular type of cell but also of reproducing the counterparts of all cells within a single entity which then takes the place of the one gone out of existence. The organs to which this function is assigned are the reproductive organs. Their chief product is the ovum, a cellular unit containing the germ-plasm. In this germinal cell begins the development of every new living entity.

In the majority of living forms, however, the ovum is not capable of undergoing division unless it is energized by another cell which is known as the sperm-cell or spermatozoön. Thus, reproduction may be either asexual or sexual. The former process or parthenogenesis is confined to some of the lower and simpler types of life, while the latter is peculiar of all higher forms. In sexual reproduction the ovum represents the female element, and the spermatozoön the male element. The former consists essentially of cytoplasm which contains a considerable quantity of nutritive material, while the latter is principally composed of nuclear substance. The essence of this mechanism is the meeting and fusion of these two elements into a single one from which a new individual is then developed. This fusion by means of which two independent units are blended into one, constitutes the process of *fertilization* or *fecundation*.

In explanation of this interaction two theories have been promulgated, namely, one emphasizing the importance of the spermatozoön and one emphasizing that of the ovum. The advocates of the former are known as *animalculists* and hold that the spermatozoön is a complete animal en miniature, possessing all the characteristics of the parent but lacking a fertile medium in which to grow. This medium it seeks and finally attains by virtue of its inherent power of movement. The advocates of the second view, who are known as *ovists*, believe that the ovum contains all the essentials of the full grown organism, but needs a stimulus to make it develop. This impetus is given to it by the spermatozoön. In accordance with this view the ovum may be likened to the bud of a plant which unfolds its leaflets and begins to grow as soon as the proper stimuli have been received by it. Both these conceptions are based upon the idea that either the spermatozoön or the ovum are preformed and hence, they may be collectively referred to as the *theory of preformation*. Subsequent investigation, however, has shown that the spermatozoön as well as the ovum are but single cells and have a perfectly definite life history. Both originate in the germinal cells of two separate individuals, and both pass through definite preliminary changes before they actually attain their maturity. Furthermore, while the part played by them in fertilization is not exactly the same, their purpose is identical, *i.e.*, both strive to produce a new individual. Consequently, neither can be said to be more important than the other.

It must be admitted, however, that we are still in ignorance regarding the physiological principle underlying this fusion of the germinal elements. Harvey and others have advocated the view that the ovum is animated by the spermatozoön and is thereby made to develop. This idea is embodied in the so-called *dynamic theories* of Spencer, Bütschli, and Hertwig, which assume that protoplasm becomes increasingly inactive and finally requires fertilization to imbibe it with a new force developed under different conditions. This process, therefore, could

be compared with the rejuvenation effected in "senile" protozoön by the method of conjugation. A somewhat different explanation is made possible by the suggestions of Trivianus, Brooks, and Weismann, that fertilization is essentially a *process by means of which variations* are produced in consequence of the acquisition of secondary elements, insuring a constant mingling and repeated renewal.

The Fertilization of the Ovum.—The physiological principle underlying sexual reproduction, is the process of fertilization effected by the fusion of the two germ-cells, one of which is of maternal and the other of paternal origin. In most cases, this union takes place within the body of the mother, but may also be accomplished in an outside medium which is accessible to both the female and male germ-cells. The manner in which these elements are brought together differs greatly in different animals, and hence, the subsequent discussion pertaining to the mechanics of sexual reproduction, must necessarily be restricted to an enumeration of the functions of the different sexual organs of the mammals. The minute changes, however, are usually studied in the eggs of the lower forms, for example, in those of the sea-urchin and the thread-worm.

Subsequent to the discovery of the spermatozoön by Hamm (1677), Leeuwenhoek expressed the idea that this element must penetrate the egg, an assumption which was later on confirmed by Spallanzani (1786), Newport (1854), and Pringsheim (1855). It seems, however, that only the head of the spermatozoön actually takes part in the fertilization, because in some animals, such as the echinoderms, the tail remains entirely outside the egg. But it is also true that the eggs of the molluses, insects, nematodes and some annelids frequently display the tail of the spermatozoön within their cytoplasm, forming here a delicate coiled up structure. At the time of contact between the male and female elements, the ovum produces two minute globular masses at its upper extremity which are known as the *polar bodies*. Since these projections take no part in the subsequent changes but degenerate and may make their appearance even before the entrance of the spermatozoön, it seems that they merely indicate that the egg has reached its mature state and is ready to receive the male sperm-cell. In all probability, a place of least resistance is formed by this means, through which the spermatozoön first arriving in this vicinity, is enabled to enter. Immediately upon conception, a tough envelope, the vitalline membrane, is developed around the ovum, thereby preventing the entrance of those spermatozoa which may have reached their destination during the interim. As soon as the head of the successful spermatozoön has been lodged in the cytoplasm, the tail atrophies and disappears. Now follows a gradual enlargement of the former and the breaking up of its chromatin material into a thread-like formation and its characteristic number of chromosomes. The egg then embraces two nuclei (Hertwig, 1875), one of which is of paternal and the other of maternal origin. This is the crucial point of fertilization, because these male and female pronuclei, containing

FIG. 532.—1, 2, 3. DIAGRAMS ILLUSTRATING THE SEGMENTATION OF THE MAMMALIAN OVUM (ALLEN THOMSON, AFTER VAN BENEDEN). 4. DIAGRAM ILLUSTRATING THE RELATION OF THE PRIMARY LAYERS OF THE BLASTODERM, THE SEGMENTATION-CAVITY OF THIS STAGE CORRESPONDING WITH THE ARCHENTERON OF AMPHIOXUS (BONNET).

equal amounts of chromatin of dual origin, now approach one another and are joined or even fuse into one which is known as the cleavage or segmentation-nucleus. Shortly afterward the nuclear membrane disappears, a spindle is developed and a number of chromosomes arise from the cleavage-nucleus which in all probability have been derived in equal proportions from the two germ-nuclei. Fertilization is then rapidly followed by the division of the cell, the stimulus for it having been given by the centrosome which thus becomes the controlling agent in the further development of the embryo.

The successive divisions now following eventually give rise to numerous cells which arrange themselves in the form of either a spherical mass (morula) or a circular disc. In the former case, the center finally becomes hollow, forming the blastula. These cells then arrange themselves as a uniform layer which is known as the blastoderm. Somewhat later the blastula is invaginated (gastrula), thereby giving rise to two layers of cells, namely, an outer or ectoderm, and an inner or entoderm. The next step in this development is the formation of a third or median layer which is known as the mesoderm. In this way, the foundation is laid for a physiological division of labor, because from these three layers are derived the various organs of the adult individual. But the question of whether this mesoderm arises from the entoderm or from the ectoderm, has not been definitely settled as yet; in fact, it seems that it may originate from either. This differentiation of the germinal layers having been completed, *genesis* begins. The ectoderm or epiblast eventually gives rise to the central nervous system and the epidermal tissues, while the mesoderm or mesoblast originates the vascular, muscular and bony tissues as well as the generative and excretory organs, exclusive of the bladder, the first part of the male urethra and the female urethra. The entoderm or hypoblast forms the epithelium of the intestines as well as that of the intestinal glands and respiratory passage, the prostatic portion of the male urethra and the entire female urethra.¹

Parthenogenesis and Artificial Parthenogenesis.—Sexual reproduction necessitates the conjugation of two cells and the fusion of their nuclei. During this process the number of the chromosomes in the germ-cells is reduced to one-half the number characteristic of the somatic cells.² In a few instances, however, the ovum alone is capable of producing a new individual; but this mode of reproduction, which is known as parthenogenesis, remains confined to the simplest forms, such as the insects and the lower crustaceans and rotifers. It should also be noted that in some species parthenogenesis alternates with sexual generation, but the variability of the non-sexual offsprings is as great as that of the sexual ones. This fact speaks against the conception of Weissman, according to which the purpose of sexual reproduction is to induce variations.

In parthenogenesis the stimulus is given by the second polar body which thus takes the place of the spermatozoön. The ovum develops

¹ For a more detailed discussion of the process of fertilization the reader is referred to textbooks on Embryology, and especially to such books as Wilson's "The Cell in Development and Inheritance." This brief account has been inserted here merely to serve as a connecting link between the substance of this chapter and that of the succeeding.

² Van Beneden, *Arch. de Biologie*, iv, 1883.

with the chromosomes of the female pronucleus, *i.e.*, with one-half the number allotted to it in sexual reproduction. A similar result is obtained during the development of denucleated portions of mature ova when fertilized by spermatozoa. Since the nucleus is the essential factor, the development occurs in the former case without admixture with the male element and, in the latter, without the properties of the female.

Parthenogenesis may also be incited artificially. Shortly after Bataillon succeeded by means of mechanical impacts in causing unfertilized eggs to develop, J. Loeb¹ showed that the fertilized egg of the sea-urchin may be prevented from developing by abstracting the oxygen from the sea-water by means of KCN or NaCN. In 1899, this author found that the unfertilized eggs of the same species may be made to develop into larvæ by exposing them during a period of two hours to hypertonic salt solutions.² By altering the medium by the addition of formic or lactic acid he finally succeeded in causing the unfertilized ova of this and other species to develop their membrane as well as those initial changes which normally require the entrance of the spermatozoön. After their exposure to the aforesaid acids, the eggs were transferred into concentrated sea-water and subsequently into ordinary sea-water. Loeb suggests that the action of the spermatozoön is chemical in its nature, because it brings a certain substance into the ovum which is capable of inciting therein a definite chemico-physical reaction. The nature of this substance is still unknown, although repeated attempts have been made to isolate it. The eggs of the sea-urchin, however, have yielded upon extraction with a hypotonic salt solution and ether a substance which possesses strong fertilizing, agglutinating and cytolytic properties. Furthermore, a chemical substance has been isolated from the head of the Rhine salmon which consists of nucleic acid and a protamin. It is known as salmin. Similar substances are the clupein of the spermatozoa of the herring, and sturin from those of the sturgeon.³

The Law of Mendel.—The general conception is that the perplexing multiformity among animals and plants is due to the propagation of established forms by heredity, and that new types find their origin in variation. Darwin's "Origin of the Species" is the first attempt to analyze these phenomena in a rational way and to refer them to natural selection, in accordance with the practice of breeders and experimental botanists to fix characteristics and to produce new ones by interbreeding and grafting. In this case, heredity may be amplified by the adaptation of the individual to dominating conditions, as is clearly depicted by the struggle for existence "and the consequent survival of the fittest." Herbert Spencer, in particular, has made use of this hypothesis in explaining many structural and functional characteristics of

¹ Pflüger's Archiv, lxii, 895, 249.

² Untersuchungen über künstl. Parthenogenese, Leipzig, 1906.

³ Burian, Ergebn. der Physiol., i, 1904.

animals and plants. Moreover, stimulated by the close similarity between the changes presented by the developing ova of widely different species, Hæckel formulated his *Gastraea-theory* which states that all forms of blastoderms, consisting of two germinal layers, may be regarded as a modified simple gastrula. In the same way as the gastrula is the beginning of the formation of a single individual, so may an animal of similar simple construction be considered as the ancestor of all multicellular forms. While this view has been widely disseminated, it lacks confirmation, because it has not been proved that a gastrula gives rise to any other entity than that from which it has arisen. Furthermore, the preceding discussion pertaining to the fertilization of the ovum must have shown that the differentiation really takes place much sooner, *i.e.*, at the time of fusion of the pronuclei.

The Darwinian theory of evolution is based upon slowly developing anatomical peculiarities to which have been added certain data derived from artificial selection. Thus, an experimental element was introduced for the first time which, however, was again lost sight of later on. Opposed to this contention is the theory of mutation which is founded upon phenomena of cell-life.¹ Since racial characteristics are no doubt mapped out in the segmenting ovum, all homologies or similarities appearing later on, must find their origin in the material substance of the fertilized egg. Quite similarly, any modification in the germinal arrangement must give rise to mutations which characterize evolution.

In sexual reproduction it may be surmised that the carriers of the characteristics are the chromosomes, which thus impart to the new individual the peculiarities of its parents. This transfer, however, is not always effected in a proportional measure, but often favors more particularly the male or female parent. We have seen that the mitosis then occurring, is associated with a reduction of the number of chromosomes, and hence, any variation shown by the offsprings may be referred to the qualitative differences in the chromosomes which have been formed during the development of the ovum. The manner in which gross as well as minor characteristics may be transmitted has been more fully illustrated by the results of an elaborate series of experiments performed by Mendel² upon different varieties of peas. The bearing of these experiments, however, has not been fully appreciated until about the year 1900. At this time DeVries found that the seeds of Lamarck's primrose, sown in his experimental garden, gave rise not only to a small percentage of the same type but also to new types of which he recognized seven. When self-fertilized, these mutations not always bred true to their type, but produced at times new varieties. Mendel's first experiments were carried out upon peas.

¹ Buffon, *Historie naturelle*, 1755; Lamarck, *Rech. sur l'origination des corps vivants*, 1802; St. Hilaire, *Princ. de philosophie zoologique*, 1830; Weissman, *On germinal selection as a source of definite variation*, 1896, and DeVries, *Ernährung und Zuchtwahl*, *Biol. Zentralbl.*, xx, 1900.

² *Versuche über Pflanzenhybriden*, Brunn, 1866.

On crossing a plant of a tall variety with one of a dwarf type, he noted that the seeds obtained from them gave rise exclusively to tall plants. When the latter were then recrossed among themselves, the result was 75 per cent. of tall and 25 per cent. of dwarf plants. The subsequent crossing of the latter with one another yielded only dwarf plants through successive generations. The former, on the other hand, fell into two groups, because while 25 per cent. of them continued to yield tall types, the other 50 per cent. gave rise to 75 per cent. of tall and 25 per cent. of dwarf plants. Mendel explained these results by stating that characters are either dominant or recessive. In the preceding example, the tallness is dominant and the dwarf condition recessant.

This principle may be made clearer at the hand of the following example: If a gray (*A*) and white (*B*) mouse are crossed, the offspring (C_1) will be all gray. If the gray mice are now bred to each other, the young (C_2) will be either gray or white in the proportion of 3:1. On crossing the white of this generation, only white offspring will be obtained throughout. The gray individuals, on the other hand, will give rise to one-third of gray and two-thirds of white offsprings. On recrossing the former only gray young are gotten, while the latter yield both white and gray. From the white of this last generation only pure white are obtained, while the gray may be either pure gray or gray-dominant-white recessives *A* (*B*).

In applying Mendel's Law to animals, it may be assumed that the two kinds of germ-cells are individualized as dominants and recessants or that the germ-cells of the hybrid are alike, *i.e.*, that they contain both dominant and recessive characters which are then either brought forth or suppressed during fertilization in consequence of certain external and internal factors. While the former explanation is the more simple, it nevertheless fails to account for certain phenomena, as does, in fact, Mendel's Law itself. Thus, the crossing between members of the white and black races of man does not give rise to either type, but to an intermediate progeny, showing various degrees of admixture.

CHAPTER XCIV

THE MALE AND FEMALE REPRODUCTIVE ORGANS

The Testicles.—The reproductive organs of the higher animals may be divided into two classes, namely, those actually producing the generative elements, and those serving as a means of bringing these two elements together. The former embrace the testes and ovaries, and the latter, the penis, seminal ducts, vagina, uterus and Fallopian tubes. The essential sexual organ of the male comprises the testes, two oblong glands, each of which measures about 4 cm. in length, 3 cm. in breadth and 2 cm. in thickness it weighs 15 to 25 grams. These organs are contained in a sac-like appendage, the scrotum, which is divided into two

halves by a médian raphé and incomplete septum. The skin, with the underlying *dartos*, assumes a corrugated appearance under the influence of cold, this effect being due to the contraction of the smooth muscle cells which are scattered throughout this tissue. The activity of these muscle fibers is greatly influenced by the general condition of the body, their tonicity and contractility being much diminished during states of depression and in old age. The areolar envelope of the testicle embraces scattered bundles of striated muscle which constitute the so-called *cremaster muscle*. They are continuous with the lower fibers of the internal oblique muscle, and their contraction shortens the funiculus and raises the testicle. Their action is controlled by the genital branch of the genito-femoral nerve.

In cross-section each testis is seen to be enveloped by a dense fibrous membrane, or *tunica albuginea*, which enters its interior as radial septa and divides it into numerous compartments. These spaces are occupied by the secreting

FIG. 533.—DIAGRAMMATIC VIEW OF THE SEMINIFEROUS TUBULES.

A, Tunica albuginea; S, septula; M, mediastinum, and vasa recta; R, rete testis; E, vasa efferentia; Ep, epididymis; G, globus major; GM, globus minor; D, vas deferens.

elements, the *seminiferous tubules*, all of which are arranged divergently from a common center, formed by the vasa recta. Each tubule pursues at first a very circuitous course, but straightens out as soon as it approaches the mediastinal septum, where it unites with others into from 20 to 30 straight tubes or *vasa recta*. The latter traverse the mediastinum to form the *rete testis*. The total number of seminiferous tubules has been estimated at from 800 to 1000. When completely unfolded, each measures from 30 to 50 cm. in length, and possesses a diameter of 0.3 mm. Centrally to the rete, the small ducts again become convoluted, and unite to form the *vasa efferentia*. In this way is formed the *epididymis*, a convoluted single duct measuring about 7 m. in length and 0.4 mm. in diameter. This collecting channel descends behind the testicle to its lower border, where it passes over into the *vas deferens*, an ascending, rather straight tube which traverses the abdominal ring and, by following the under surface of the base of the bladder, eventually terminates in the prostatic division of the *urethra*. The vas deferens is about 60 cm. in length and possesses a diameter of from 2 to 3 mm.

This recurrent course of the seminal collecting tube finds its origin in the fact that the testes are developed in the peritoneal cavity from the germinal epithe-

lium, and descend later on through the abdominal ring into the gradually enlarging scrotum. Their descent through the ring takes place shortly before birth. This fact also accounts for the peculiar blood supply of these organs which is derived from the abdominal aorta by the slender and unusually long spermatic arteries. The venous return is effected by the spermatic veins, the right one entering the inferior cava directly, and the left one, the left renal vein. Inasmuch as the latter joins the renal almost at right angles, it cannot discharge its blood with absolute freedom, a condition which in later years often gives rise to a venous engorgement and a lower position of the corresponding organ.

FIG. 534.—DIAGRAM OF THE FLAGELLATE SPERMATOZOON. (From Wilson, "The Cell in Development and Inheritance.")

The Development and Character of the Spermatozoa.—Up to the time of puberty, the seminal tubules are filled with cells containing unusually large nuclei. Among these are found the *spermatogonia* which then discontinue their divisions and rapidly develop into the so-called *spermatocytes*. From these arise by hetero-mitosis the *spermatids* or sperm-cells, and from these in turn the adult *spermatozoa*. Each spermatocyte, however, divides into two daughter-cells and the latter in turn into two, so that really four spermatids and spermatozoa are developed from each primary spermatocyte. The nuclear material of the spermatid is transformed directly into that of the spermatozoön, while its cytoplasm is apportioned to the tail. In some cases, however, the centrosome of the spermatid is converted into the middle piece and the axial filament of the tail. This process, therefore, is not a mere division of the cell, but a reduction-mitosis, the chromosomes being reduced by one-half. In this regard, the formation of the spermatozoön is analogous to the maturation of the ovum during the projection of the polar bodies, but since the union of these two elements eventually restores the original number of chromosomes, the spermatozoön and ovum really supplement one another.

When fully formed, the spermatozoa are forced into the epididymis and vas deferens, but since they do not become motile until they have reached the former, their progress through the more distal channel must be effected by the lining cells of the seminiferous tubules and differences in pressure. In the vas deferens, they are then able to unfold their power of movement more fully and, besides, this tube greatly facilitates their progress by its peristaltic contractions as

well as by the action of the cilia-like appendages of some of its lining cells.

The *spermatozoön* is a complete cell, consisting of a nucleus and cytoplasm. In many cases, however, it is $\frac{1}{100,000}$ times smaller than the germinal cell of the opposite sex, the ovum. It has the appearance of a minute tadpole and presents a nucleus which forms the principal portion of its conoid and slightly flattened head, an apical piece or acrosome at the front of the head, a middle piece directly behind the head, and a long slender tail or flagellum. Its total length measures from 50 to 80 μ .¹ Physiologically considered, its nucleus derives its importance from the fact that it contains the chromatin, while its middle piece represents the centrosome element which serves as the stimulus to division. Its apical piece is of importance because it enables the spermatozoön to bore its way into the ovum, and its tail because its contractile substance furnishes the motile power by means of which this chemical complex is enabled to reach the passive ovum.

The formation of spermatozoa begins at the time of *puberty* or *sexual maturity*, i.e., in temperate climates at about the fifteenth year. Some of

FIG. 535.

FIG. 536.

FIG. 535.—DIAGRAM TO REPRESENT THE PROGRESSIVE SERPENTINE MOVEMENTS OF THE TAIL OF THE SPERMATOZOÖN.

FIG. 536.—DIAGRAM OF THE BLADDER, PROSTATE GLAND, ROOT OF PENIS, ETC.

Cl, Part of base of bladder covered by peritoneum, separated by a dotted line from a triangular space left uncovered by that membrane; *V*, ureter; *S.V*, seminal vesicle; *ED*, ejaculatory duct; *P*, prostate; *M*, membranous part of the urethra; *B*, bulb; *C.S*, corpus cavernosum urethræ; *C*, crus penis; *C.G*, Cowper's gland. (*J. Symington*.)

the adjunct powers of the sexual mechanism, however, may have been active for some years before this time; for example, the erection of the penis and sexual desire. Thus, the only definite sign of maturity is the presence of fully developed spermatozoa in the semen. This change is associated as a rule with a greater stability of the body as a whole. The voice becomes deeper, owing to a more rapid growth

¹ Eberth, in *Bardleben's Handb. der Anatomie des Menschen*, Jena, 1904.

of the larynx, while the legs, arms and other parts cease their often very prolific growth and increase in compactness rather than in length.

The Seminal Vesicles. The Semen.—Shortly before its entrance into the prostatic urethra, the vas deferens receives a duct from the *vesicula seminalis*, and is now known as the *ejaculatory duct*. Each seminal vesicle is about 4 cm. in length, pyriform in shape, and occupies with its fellow-organ the under surface of the bladder, directly behind the prostate gland. Its wall consists of an external fibrous coat, a middle muscular coat and an internal mucous coat. The mucosa is beset with numerous tubular albuminous glands which add a stringy constituent to the semen, consisting chiefly of globulins. Since the semen becomes more fluid upon standing, it seems that these globular masses, which have been added to it by the seminal vesicles, merely serve the purpose of giving a greater volume to it. In fact, in some animals this material is made to clot through the agency of a ferment derived from the prostate gland. Obviously, this would tend to obstruct the orifice of the vagina and thus prevent the loss of spermatozoa. But it cannot be said that the seminal fluid, plus the spermatozoa and testicular secretion, constitutes the entire semen, because this medium receives in addition the products of the prostatic and urethral glands.

The *prostate gland* attains the size of a chestnut and consists of 30 to 50 lobules with 15 to 30 ducts which open near the orifice of the ejaculatory duct. The prostatic secretion is thin, cloudy, slightly alkaline, and contains albumin but no mucin. The *urethral or Cowper's glands* are represented by two small globular masses, one on each side of the prostate, which empty their product into the cavernous portion of the urethra. Their ducts measure 3 to 4 cm. in length. Their secretion is alkaline and rich in mucin. Droplets of it appear sometimes in the meatus urethrae after micturition or after sexual excitement which has not actually led to an emission of semen.

The semen is grayish-white in color, and possesses a mucilaginous consistency. Its specific gravity varies between 1.027 to 1.040. Its very characteristic odor is derived from the spermin of the prostatic secretion. The amount discharged during one ejaculation varies between 1 and 6 c.c. in accordance with the sexual activity of the individual, and each emission may furnish as many as 226,000,000 of spermatozoa.¹ These elements are formed constantly and are then stored in the seminal vesicles and adjoining tortuous portion of the vas deferens. The fact that the liquid here collected contains about 70,000,000 of spermatozoa per cubic centimeter, although only one of them is sufficient to fertilize the ovum, shows how liberal and fixed in its purpose nature actually is when the propagation of the species is at stake.

The Erectile Tissues of the Male.—The transfer of the semen into the seminal receptacle of the female is made possible by the act of

¹ Lode, Pflüger's Archiv, 1, 1891, 278.

erection of the penis, the male organ of copulation. It is composed chiefly of cavernous tissue which is arranged in three long and somewhat cylindrical masses, forming the corpus spongiosum below and the two corpora cavernosa, one on each side, above. The former is traversed by the urethra and terminates anteriorly in a conical structure, the glans penis. Externally, these bodies are enveloped by fibrous sheaths and a thin layer of very movable and distensible skin, which is then reflected upon the glans penis to form the prepuce. The erectile tissue of which these bodies are composed, is made up of cavernous spaces which are really venous sinuses lined with a layer of flattened epithelium. Their walls consist of membranous partitions which are derived from the external fibrous investment, the tunica albuginea, as well as from the median septum of the penis. In this way, a spongy network of connective tissue is formed which is much denser near the circumference than near the center. The central spaces, therefore, are larger than the outer ones, but all of them are supplied with blood from branches of the internal pudendal artery through capillaries which are rather more widely open than those of other tissues.

The erection of this tissue is dependent upon a dilatation of these afferent channels through which the blood is then poured freely into the lacunæ, but since the venous collecting tubules begin with a narrow orifice which is strengthened by rings of smooth muscle tissue, the outflow is somewhat hindered both in a mechanical way as well as by an active constriction of these sphincters. Consequently, the erection of the penis cannot be regarded as a pure vaso-dilator phenomenon, but as an active venous retardation which is brought about chiefly by the contraction of those muscle cells with which the outlets of the several blood-spaces are beset. In addition, it is entirely probable that the action of this intrinsic muscle tissue is materially strengthened by the contraction of certain extrinsic muscles, such as the ischio and bulbo-cavernosi. By compressing the larger collecting channels, these muscles tend to raise the venous pressure without actually blocking the return of the blood. Meanwhile, the inner walls of the cavernous spaces are fully exposed to the arterial blood-pressure,¹ which causes them to move outward as far as their tough fibrous constituents as well as the fibrous investment of the entire organ will allow.

The length of time during which copulation must be continued in order to give rise to an ejaculation of the semen differs greatly with the condition and type of the animal. It is safe to assume, however, that the erection of the penis cannot be attained by vaso-dilatation alone, because a reaction of this kind is neither sufficiently intense nor lasting. Nor can it be due to venous stagnation alone, because the erected organ does not become cyanosed and retains a higher temperature throughout this act. These facts unmistakably point toward a more copious blood supply and greater through-flow and not merely

¹ François-Frank, Arch. de Physiol., 1895, 122.

toward a more abundant content in blood at any one time. This conclusion is strengthened by the fact that in priapismus this organ may retain its erected condition for hours and even for days without showing an actual impairment of its tissues or gangrene. Naturally, the size and shape of the erected organ are determined not only by the distention of the cavernous spaces, but also by the arrangement of its gross anatomical structures, such as its dorsal fascia and the fascia situated in the vicinity of its base. The former acts in the manner of a ligament. Since it is shorter than the one investing the under surface of this organ, the dorsal aspect of the erected penis must exhibit a decided concavity. This change in its shape imparts to it a greater penetrating power and increases its receptive power to stimuli, because it tends to retract the prepuce and to uncover the tactile receptors of the glans penis. During this period it is quite impossible to void urine, because the sphincter vesicæ remains firmly closed. Not until the erection has ceased does this sphincter regain its power of relaxation.¹

The reflex center controlling this act is situated in the lumbar segment of the spinal cord. The corresponding autonomic fibers leave this structure in the first to third sacral nerves to form the pelvic plexus and *nervi erigentes* and *cavernosi*. The fact that the latter contain vaso-dilator fibers to the penis has been proved by Eckhard, Loven and others by stimulating them electrically. Afferently, this reflex center may be activated by stimuli applied to the genitals directly, as well as by stimuli received from other sense-organs and the cortical association centers.

The Act of Ejaculation.—The discharge of the semen is initiated by a powerful peristalsis of the vas deferens, seminal vesicles and ejaculatory duct which forces the secretion into the urethra. Here it is prevented from entering the deeper urethra by the sphincter vesicæ² and is mixed with the secretions of the prostate and Cowper's glands. The latter are poured into the urethra in the hollow at each side of the *colliculus seminalis*. Then begin the rhythmic contractions of certain striated muscles which, however, are not under the control of the will. Chiefly involved in this process are the *ischio-cavernosus*, the *bulbo-cavernosus* and the *sphincter urethræ membranaceæ* or *sphincter of Henle*.

The act of ejaculation is controlled by a reflex center which is situated in the lumbar segment of the spinal cord. The latter may be activated by afferent stimuli arising in the genital organs and evoked chiefly in Krause's corpuscles with which the glans penis is abundantly supplied. Other sense-organs, such as the general cutaneous receptors, the retina, and organ of Corti may also be involved, but only in so far as their impressions give rise to erotic associations. In the absence of peripheral stimuli, the activation of the psychic centers may lead to "spontaneous" emissions, those occurring in consequence of dreams

¹ Zeissl and Holzkmacht, *Wiener med. Blätter*, 1902.

² Walker, *Archiv für Anatomie*, 1899.

being called pollutions. Among the nerves concerned in the acts of erection and ejaculation may be mentioned the *nervus pudendus*, *nervus erigens*, and *nervus ileo-inguinalis*. The first sends one of its branches, the *nervus perinei*, to the ischio and bulbo-cavernosi, the bulbos urethræ and the mucous membrane of the upper urethra. This nerve, therefore, is the one controlling ejaculation. Another of its branches, the *nervus dorsalis penis*, innervates the skin, prepuce, corpora cavernosa, and outer portion of the urethra. This nerve, therefore, conveys sensory impulses from the largest part of the penis. The *nervus erigens*, as has been stated above, is chiefly vasomotor in its function, while the *ileo-inguinalis* innervates the base of the penis.

The Ovaries.—The essential reproductive organ of the female is represented by the ovaries, two flattened, more or less almond-shaped bodies which are situated in the upper part of the pelvic cavity in a slight depression in the obturator muscle. Although subject to considerable fluctuations, the adult ovary measures 2.5 to 5 cm. in length, 1.5 to 3 cm. in breadth, and 0.6 to 1.5 cm. in thickness. In cross-section each organ is seen to be made up of two portions, a cortex and a medulla. The former varies in thickness, becoming thinner with advancing years, and consists of connective tissue containing isolated primordial and Graafian follicles. The central medullary portion is made up of loose connective tissue containing large numbers of blood-vessels and smooth muscle cells.¹

In the child, the greater portion of the ovary is composed of cortical substance which is closely packed with primordial follicles in different stages of development. This is also true of the ovary of young women, but the follicles are then more widely separated from one another by layers of connective tissue of varying thickness. Each follicle consists of an oöcyte surrounded by a single layer of epithelium and measuring from 48 to 69 μ in diameter. At birth each ovary contains at least 100,000 oöcytes, while at puberty it embraces only from 30,000 to 40,000; but even this number is more than sufficient to supply the necessary ova for fertilization, because only one of them is discharged during each menstrual period. It may also happen that one of these follicles contains two and more distinct ova, a fact which has been made use of in explaining multiple pregnancies.

These primordial follicles eventually develop into the mature Graafian follicle, a process which begins at birth and does not cease until the menopause has terminated the sexual life. To begin with, the spindle-shaped epithelial investment is changed into a single layer of cuboidal cells which then proliferate rapidly until the central ovum has become enveloped by several layers of epithelial cells. By the degeneration of certain ones of these cells a space is eventually formed around the ovum which becomes filled with fluid, the liquor folliculi. The ovum itself grows larger constantly and is gradually pushed to one side, where it becomes surrounded by a layer of cells, forming the discus proligerus. Its nucleus undergoes important changes which finally terminate in the formation of the first polar body, a deposition of yolk granules in the cytoplasm, and the formation of a thin investment, the

¹ Clark, Contrib. to the Science of Med., Johns Hopkins Univ., 1900.

zona pellucida. The entire follicle is marked off against the now very vascular connective tissue stroma by the membrana granulosa.

The Mature Graafian Follicle.—Beginning shortly after birth, the developing primordial follicles pass from the inner realm of the cortex toward its periphery, but do not actually reach the surface. Later on, however, the more superficial ones pursue the same course and actually appear externally in the form of projecting vesicular bodies, the diameter of which varies between 2 and 15 mm. The outer wall of these vesicles is thin and nearly bloodless (stigma), while their remaining investment is really more vascular than previously. At this time, therefore, the projecting Graafian follicle consists of a

FIG. 537.—GRAAFIAN FOLLICLE OF MAMMALIAN OVARY.

ov, Ovum; dp, discus proligerus; lf, liquor folliculi; ch, theca; gr, membrana granulosa. (Prenant and Bouin.)

connective tissue investment, or theca follicula, an epithelial covering, or membrana granulosa, the ovum, and the liquor folliculi. The ovum itself now measures 0.2 mm. in diameter, as against 48 to 69 μ when first formed, and contains large numbers of irregularly shaped and highly refractive granules, the so-called deuterooplasm. Its nucleus or germinal vesicle presents a well differentiated nucleolus, or germinal spot. It is also of interest to note that the connective tissue stroma gives rise at this time to a peculiar type of cells which contain a yellowish pigment and are destined to play an important rôle later on in the formation of the corpus luteum.

The Corpus Luteum.—According to Clark,¹ the rupture of the Graafian follicle is brought about by complex changes in the vascularity of the ovary, leading to a congestion of the entire organ. In consequence of this increased tension, the follicle is pushed far outward. The stigma of its outer wall becomes necrotic and bursts, allowing the liquor as well as the ovum and a part of the torn *membrana granulosa* to escape into the tube. The walls of the empty follicle then collapse, but are distended again by blood derived from the vessels of the theca. To begin with, therefore, the corpus luteum is represented by a ruptured Graafian follicle, filled with blood and invested by a layer of yellow lutein cells of the theca. The latter multiply rapidly and presently enter the hemorrhagic extravasate which they occupy completely with the exception of a small central area. Connective tissue strands and blood-vessels follow them in increasing numbers so that the corpus finally assumes the appearance of an organized and growing structure. Very soon, however, retrogressive changes set in which terminate in a hyaline degeneration of the lutein cells and their final absorption. This obliteration of the corpus luteum takes place more rapidly in young persons, because the circulation of the adult ovary has lost much of its original vigor. Eventually, the corpora appear merely as small whitish granules resembling scar tissue. They are then known as the corpora fibrosa or albicantia.²

It is to be emphasized, however, that it is not real scar tissue; in fact, the reason for the formation of the corpora lutea is to prevent the conversion of the ovarian parenchyma into a tissue of this type which would effectively prevent the formation and discharge of other ova.³ Besides, the corpus luteum seems to furnish an internal secretion which is intimately concerned with the future development of the ovum.⁴ Thus, it has been noted by Fränkel that the next succeeding menstruation invariably fails to take place if the corpus luteum has previously been destroyed by means of a cautery. Further evidence to show that it is a temporary gland, is presented by the fact that its atrophy and degeneration are closely connected with the fertilization of the ovum. If the latter is not fertilized, this retrogression will be completed in the course of 2 or 3 weeks, while if it is fertilized, the consummation of this process may require 6 months and longer. For this reason, it is customary to speak of true and false corpora lutea. The former is larger and persists until the development of the ovum is well advanced, whereas the latter is fully reduced within a short time after the menstrual period. According to Miller, it is possible to distinguish between these corpora by histological and micro-chemical

¹ Johns Hopkins Hosp. Rep., 1898.

² Fränkel, *Archiv für Gynec.*, lxxviii, 1903, 438, and xci, 1910, 705; also: Meyer, *ibid.*, c, 1913, 1, and Ruge, *ibid.*, c, 1913, 20.

³ Marshall, *Physiol. of Reproduction*, London, 1910.

⁴ L. Loeb, *Jour. Am. Med. Assoc.*, xlv, 1906, 416.

means, because neutral fat is readily demonstrable in the corpus luteum of menstruation.

Menstruation.—The process of menstruation is a periodic change in the life cycle of the female which is most plastically betrayed by a discharge of blood from the genitals, derived chiefly from the mucous membrane of the uterus. In general, it may be said that this phenomenon appears for the first time at puberty and is continued thereafter at intervals of 28 days until about the forty-fifth year. This statement would imply that it begins in temperate climates at about the twelfth year and in cold climates at about the fifteenth year, but much depends upon the physical condition of the individual as well as upon her sexual development and mode of life. Thus, we are reminded at this time of the child-woman of certain sections of India, where menstruation is regarded as a disgrace and where corresponding measures are taken to prevent it with not especially flattering results to the offspring nor to the mother. In fact, Haller mentions a case of a child-mother who menstruated regularly from her second year and gave birth to a child at the age of nine.

Before the first menstrual period, the approaching sexual maturity betrays itself by a more rapid growth. The pelvis assumes a typically feminine shape, the mammæ become enlarged and hair begins to grow upon the genitals as well as in the axillæ. Although prone to be irregular at first, the menses are repeated as a rule every 28 days, but certain variations in this time are by no means uncommon. The hemorrhagic discharge sets in slowly, reaches a maximum about the second or third day, and then gradually subsides. Consequently, not more than 4 or 5 days are usually consumed by it. In our country, menstruation ceases at about the forty-fifth year, but it has been noted to disappear as early as the twenty-eighth year and as late as the sixty-third year. It is by no means a rare occurrence that women of fifty and over bear children. The cessation of the menstrual flow is the expression of a series of changes constituting the menopause. Underlying these changes are a series of important metabolic alterations, the completion of which often requires several years and renders the woman particularly susceptible to pathological processes of all kinds. During the period intervening between puberty and the menopause, conception may take place at any time. In rare instances, however, this result has also been known to have been attained long before sexual maturity as exemplified by the changes just enumerated. Menstruation ceases immediately upon conception and does not recur until after the termination of the periods of pregnancy and lactation.¹

The discharge of blood, however, does not actually constitute the menstrual period. It really begins several days beforehand, and is ushered in by a feeling of fatigue, pains in the back, headache, an increased irritability of the nervous system, an unusual tenseness and sensitiveness of the mammæ, a congestion of the vulva, and a more

¹ Ploss, *Das Weib in der Natur und Völkerkunde*, Leipzig, 1894.

copious secretion of vaginal fluid and mucus. These premonitory symptoms are followed by a hemorrhagic oozing and later on by a period of restitution which occupies almost two weeks. Consequently, only a few days of absolute functional rest intervene between the successive menstrual cycles.

The division of this process into the periods of premenstruation, menstruation, restitution, and complete rest leads us to suspect that the endometrium of the uterus retains a comparatively normal appearance only during the last stage of restitution and the succeeding period of rest.¹ During the premenstrual state it presents distinct evidences of proliferation, swelling and hypersecretion. The cells of the stroma lose their elongated shape and become more rounded. The capillaries are greatly distended with blood which in turn gives rise to a hyperplasia of the uterine glands. A few days later blood begins to escape from the superficial vessels and forces its way into the lumen of the uterine canal, and through the constricted orifice of the cervix into the vagina. But this hemorrhagic extravasation is not associated with any considerable destruction of tissue; in fact, the uterine lining remains rather intact, although it may be perforated here and there and even partially loosened from the underlying layers by spaces which are filled with blood. In most instances this congestion also involves the tubes, ovaries and external genitals, but these organs do not contribute to the hemorrhagic discharge and hence, menstruation is to be regarded essentially as a phenomenon of the uterus. The quantity of blood lost during this period may amount to as much as 100 to 300 grams.² Under ordinary conditions, however, it is mixed with considerable quantities of mucus, which substance tends to preserve the thrombocytes and, therefore, to prolong the coagulation-time. Menstrual blood as such clots as readily as any other type of blood.

The phenomenon of heat exhibited by the lower mammals is the homologue of menstruation. It is commonly divided into four periods, namely: (a) the proestrus, during which the organs become congested and bleed, (b) the estrus, or stage of sexual desire, (c) the metestrus, or period of restitution, and (d) the anestrus, or stage of rest. Contrary to the human female, those of the other mammals take the male only during the estrus. If sexual union or conception is prevented at this time, the period for sexual intercourse gives way to the period of restitution, but recurs again after a definite interval which in bitches is 12 to 16 weeks, in the cow 3 to 4 weeks, in the sheep 2 to 4 weeks, in monkeys about 4 weeks, and in the sow 9 to 18 days.

Relation Between Menstruation and Ovulation.—Among the many theories proposed to explain the cause of menstruation is the older view that the menstrual flow is the female fluid of fertilization. Subsequent to the establishment of the fact that menstruation occurs in periodic cycles, it was then believed that it is brought on by the ma-

¹ Findley, *Anat. of the menstr. uterus*, *Am. Jour. Obst.*, xlv, 1902, and Hitschmann and Adler, *Bau der Uterusschleimhaut*, *Monatsh. für Geb. und Gyn.*, xxvii, 1907.

² Hoppe-Seyler, *Zeitschr. für physiol. Chemie*, xlii, 1904, 545.

turing of the Graafian follicle and the discharge of the ovum. Pflüger¹ sought its cause in a reflex extravasation of blood evoked by the pressure which the growing follicle exerts upon the nerves of the ovary. This view, however, was put into question by the clinical experience that ovulation and even pregnancy may result before the first menstruation as well as after the menopause.² It was also noted that conception may take place during the period of lactation, whereas the menstrual flow is then usually absent. Lastly, it has been observed by Rein³ that pregnancy is possible in dogs even after all the nerves connecting the uterus with the spinal cord have been divided. Certain experiments are also at hand to show that menstruation does not cease after the transplantation of the ovaries into some other part of the body, while ovulation is then impossible. In 1871, Sigismund advocated the view that menstruation succeeds ovulation and is the direct result of the failure of the ovum to become fertilized. It has also been stated that menstruation is a process of purification and, therefore, serves to clean out the uterus and to establish a proper substratum for the fertilized ovum to grow upon.⁴

Subsequent to the development of the hormone doctrine, Fränkel⁵ proposed the theory that menstruation is dependent upon the formation of an internal secretion by the corpus luteum which controls the blood supply of the ovary.⁶ He believed ovulation to be related to this process only in so far as the escape of the ovum initiates the formation of the corpus luteum which attains its full development about 7 days later, *i.e.*, at a time when menstruation sets in. Consequently, ovulation must take place 19 days after the last menstrual flow. This explanation has many points in its favor, and may be supported by strong clinical evidence. In the first place, it is obvious that menstruation is dependent upon some activity of the ovaries, because the removal of these organs gives rise to an artificial menopause which is characterized by a cessation of the menses and an atrophy of the uterus. Secondly, this cessation of the menstrual flow does not result if the ovaries are transplanted into the uterus or elsewhere in the abdominal cavity.⁷ Thirdly, menstruation may be made to recur by grafting a piece of an ovary in the uterus or under the skin of the abdomen,⁸ and a temporary condition of estrus may be incited in mature animals by the injection of an extract of ovaries taken from

¹ Bedeutung und Ursache der Menstruation, Berlin, 1865.

² Berliner klin. Wochenschrift, 1871.

³ Pflüger's Archiv, xxiii, 1880, 68.

⁴ Bryce and Teacher, Early development of the human ovum, 1903.

⁵ Archiv für Gyn., 1910.

⁶ The dried extract of the corpora lutea of cows is made use of in the treatment of suppressed menstruation and the grave symptoms sometimes following the removal of the ovaries and premature production of the menopause.

⁷ Halban, Deutsche Gesellsch. für Gyn., ix, 1901; also: Glass, Medic. News, 1899, and Morris, Med. Rec., 1901.

⁸ Meredith, Brit. Med. Jour., 1904.

an animal in heat.¹ Having established this fact, it may then be proved that ovulation is not synchronous with menstruation. Thus, it is well known that the Mosaic Law regards Jewesses unclean during the menstrual period and for 7 days thereafter. In these women, therefore, conception must take place after this period and before the onset of the next menstrual flow. Moreover, Pinard² has shown that about three-fifths of the women who marry during the interim between two menstrual periods and miss the subsequent flow, give birth to full-term children 280 days after the beginning of the last menses. In these cases, the duration of pregnancy is less than 9 calendar months. Consequently, if ovulation takes place some time before the onset of the menstrual flow, the latter must be in the nature of a process of purification which prepares the endometrium for the succeeding ovulation. This cyclic regeneration, therefore, tends to keep the uterine membrane in a condition of irritability which enables it to respond very promptly to the stimulus brought to bear upon it by the fertilized ovum. It is thus in the best possible condition to develop the decidual membranes.

CHAPTER XCV

THE DEVELOPMENT OF THE EMBRYO

The Migration of the Ovum.—In those animals in which the ovary is enveloped by a peritoneal pouch into which the Fallopian tube opens, no special difficulty confronts us in explaining the migration of the newly formed ovum into the uterus. In those animals, on the other hand, in which the ovary and fimbriated extremity of the Fallopian tube are not in direct contact with one another, we are forced to assume that the ovum first escapes into the peritoneal spaces and then enters the tube from without. This manner of migration is exemplified by the human female. Attention was first called to this possibility by Bischoff,³ who found that animals possessing bifurcated or bicornuated uteri frequently present corpora lutea in the ovary opposite to that horn of the uterus in which the embryos are developing. Two explanations may be offered for this occurrence, namely: (a) that the ovum has penetrated the tube on the same side and has later on been forced into the cornu uteri of the opposite side, and (b) that it has migrated to the opposite side to begin with and has then entered the tube and uterine horn of the same side. The former process is called *internal migra-*

¹ Marshall and Jolly, Phil. Transact., R. Soc., London, 1905.

² Ann. de gyn. et d'obst., 1909.

³ Die Entwicklung des Kanincheneies, 1842; also Kussmaul, Von dem Mangel, Verkümmern und Überwanderung des Eies, Würzburg, 1859.

tion and the latter, *external migration*. Leopold¹ has proved that the latter process is possible by excising one ovary and the tube of the opposite side. Many of these animals became pregnant. A similar case has been reported by Kelly,² who removed the diseased left ovary and right tube of a woman, leaving the right ovary and left tube in situ. Fifteen months after the operation, this woman gave birth to a normal child. Seventeen months later, the left tube had to be removed for the relief of a ruptured extra-uterine pregnancy. Inasmuch as the ovum does not possess an inherent power of movement, its progress must be determined by outside forces, such as gravity and the action of the ciliated lining of the tube and uterus.

While much uncertainty prevails regarding the manner in which the ovum gains entrance to the tube, it seems established that external migration occurs much more frequently than has been supposed. In view of the preceding data, it would seem probable that the ovum migrates through the narrow peritoneal spaces between the pelvic viscera and may then be received by the tube of the same side as well as by that of the opposite side.

The Migration of the Spermatozoa.—In the male, the climax of the coitus is reached with the ejaculation of the semen which may or may not occur synchronously with the orgasm of the female. The latter betrays itself by an erection of the clitoris and vaginal folds, a more copious secretion of vaginal fluid by the glands of the vestibulum and the glands of Bartholini, a twitching of the external bands of vaginal muscle tissue (sphincter vaginae), and an alternate depression and elevation of the uterus. The spermatozoa deposited in the seminal receptacle, the vagina, find their way into the uterus by their own activity which consists in a lateral oscillatory progression of the head in consequence of the whip-like action of the tail. The latter, however, does not contract as a whole from side to side, but in the manner of the tail of an eel (Fig. 535). Under favorable conditions the speed attained by them may amount to 4 to 10 mm. in a minute.³ They are aided in their upward movement by the mucous secretion of the uterus which attracts them. In other words, this secretion exerts a positive chemotactic influence upon them, whereas the sour vaginal fluid affects them negatively.⁴ Secondly, it is a well-known fact that the cilia of the uterus and Fallopian tubes beat in a direction from above downward and, therefore, might retard the progress of these elements. This is not so actually, because the spermatozoa are stimulated by these mechanical impacts to greater activity and are capable of advancing even against the direction of the stream of the intra-uterine fluid. They are, therefore, positively rheotactic and thigmotactic.

¹ Archiv für Gynec., xvi, 1880, 22.

² Operative Gynec., ii, 1898, 187.

³ Lott, Anat. und Physiol. des Cervix uteri, Erlangen, 1871, and Henle, Lehrb. der Anat., Leipzig, 1890.

⁴ Chrobak, Wiener klin. Wochenschr., 1901; and Löw, Stitzungsab. Wiener Akad., 1902.

The fact that the spermatozoa are capable of making their own way through the canal of the cervix into the uterus is proved by the cases of pregnancy following incomplete coitus, and especially by the pregnancies which have occurred in women possessing perfect hymens. Nevertheless, it has been thought by Litzmann, and others, that the uterus contracts and relaxes at the height of the orgasm and actually aspirates the semen into its cavity. Moreover, Kristeller¹ has advocated the view that a mucus plug is projected at this time from the mouth of the cervix, which is then retracted, carrying with it large numbers of spermatozoa.

The Place of Meeting of the Ovum and Spermatozoa.—The view that the fertilization of the ovum is effected within the cavity of the uterus, has now given way to the belief that the meeting between the male and female sperm-cells takes place in the Fallopian tube and chiefly in its funnel-shaped outer extremity. Since the distance between this point of the generative tract and the mouth of the uterus measures only about 16 cm., the spermatozoa may reach this receptacle in less than 1 hour. In fact, the occurrence of ovarian pregnancy in woman demonstrates that these elements may even advance as far as this organ and that the fimbriated extremity of the tube is not absolutely impermeable. This view, that impregnation takes place in the Fallopian tube, also finds substantiation in the fact that living spermatozoa have frequently been found here; in fact, they have been noted to live within its lumen for an almost indefinite period of time. In the tubes of the bat, for example, they have been known to retain their activity for many months.

The Implantation of the Ovum.—After its fertilization the ovum undergoes repeated segmentation and slowly progresses into the uterus where it remains until the end of the period of gestation. It traverses this distance in about 8 days after its impregnation, having meanwhile attained a diameter of 0.2 mm. and completed the morula stage.² The earliest specimen of developing ova has been described by Bryce and Teacher.³ It measured 0.77 mm. in length and 0.63 mm. in breadth, and was about 13 days old. This one, as well as all the others representing a later stage of development, were found deeply imbedded in the decidua and hence, well removed from the cavity of the uterus. Spee,⁴ therefore, assumes that the human ovum attaches itself to the free surface of the endometrium and destroys the underlying tissue by means of a tryptic ferment.⁵ In this way it gradually sinks into the depth of the uterine decidua, its point of

¹ Berliner klin. Wochenschr., 1871.

² Grosser, *Vergl. Anat. und Entwicklungsgesch. der Eihäute und Placenta*, Leipzig, 1909.

³ Early development and imbedding of the human ovum, Glasgow, 1908; also Linzenmeier, *Archiv für Gynec.*, cii, 1914, 1

⁴ *Zeitschr. für Morph. und Anthropol.*, 1901, and *Verh. deutsch. Ges. für Gynec.*, 1906.

⁵ Gräfenberg, *Zeitschr. für Geburtshilfe und Gynec.*, 1910.

entrance being obliterated very soon thereafter by the coalescence of the edges of the opening.

Pregnancy.—With the descent of the ovum, the woman begins to exhibit very characteristic local and general signs of pregnancy. The virgin uterus is small, pear-shaped, almost solid, and only 6.5 cm. in length. At the end of pregnancy, on the other hand, it has been converted into a large thin-walled sac, measuring 32 cm. in length, 24 cm. in breadth, and 22 cm. in depth. Its volume, which now amounts to 5000–7000 c.c., has been increased 519 times, and its weight from 32 grams to 1000 grams. This hypertrophy really begins with the moment of conception, and while all of its elements are involved in this process, it affects more particularly its smooth muscle-cells. The latter increase not only in their length and thickness, but also in their number. A similar proliferation takes place in the elastic tissue and mucous membrane, which attains a thickness of almost 0.5 cm. by the time the ovum has entered the uterine cavity and of 0.75 cm. at the end of the second month after conception. At the end of pregnancy, the uterine wall shows an average thickness of only 3–5 mm. These changes account for the fact that the cervix uteri loses its firm and almost cartilaginous consistency within a few weeks after conception. A similar change is noted very shortly before the onset of each menstrual flow.

The vascularity of the ovaries is increased, but ovulation ceases as a rule during pregnancy. For this reason, it is not difficult to detect the corpus luteum formed in the place of the impregnated ovum. The vaginal wall also becomes more vascular and assumes a peculiar violet color. Its tissue is strengthened by new elements and so is that of the vulva. Possibly the most striking change is exhibited by the *mammæ* which alter their consistency and size as well as color. Already during the second month of pregnancy, these organs become tense and nodular and are permeated by numerous large veins which are sharply outlined against the lighter glandular tissue. The nipples increase in size, become more erectile and assume a much deeper color. The areola surrounding each becomes much broader, assumes a darker color, and acquires numerous globular elevations which find their origin in an enlargement of the sebaceous glands. Owing to the increased distention of the integument, *striæ* may be formed which closely resemble those noted in the wall of the abdomen of multipara. This enlargement of the *mammæ* results in consequence of the discharge of a specific hormone by the sexual organs. Quite aside from the experiments of Claypon and Starling upon virgin rabbits, which have been cited above but have more recently been criticized by Frank and Unger,¹ this conclusion is fully justified by the observations of Schants,² upon the Blazek sisters, a pygopagous twin. One

¹ *Archiv of Int. Med.*, vii, 1911, 812.

² *Gynec. Rundschau*, iv, 1910, 437.

of these gave birth to a child which was subsequently suckled by either with equally beneficial results.

The enlarging uterus also inflicts certain spatial restrictions upon the neighboring pelvic and abdominal organs. Since these changes are effected chiefly by its fundus, whereas the cervix tends to retain its previous size, a rather acute angle is finally formed between these parts, which is augmented still further as the fundus progresses upward beyond the boundaries of the pelvis. At the fourth month the upper border of the latter lies opposite a horizontal line drawn midway between the umbilicus and the symphysis pubis, at the end of the sixth month opposite the umbilicus, and at the end of 9 months almost opposite the ensiform cartilage. The intestines are forced into the lateral extents of the abdominal cavity, so that the anterior wall of the uterus comes to rest against the anterior wall of the abdomen. The linea alba is broad and sharply outlined by its glistening white color. It need scarcely be emphasized that these encroachments are responsible for a whole series of far-reaching reflex actions.

Among the latter might be mentioned the vomiting of pregnancy, minor disorders of digestion, constipation, and stagnation phenomena in the biliary passages.¹ The kidneys may be affected directly by pressure, as well as indirectly in consequence of various disturbances of metabolism. The heart is displaced and its area of dulness increased. The latter change has given rise to the statement that this organ undergoes at this time a mild hypertrophy.² The pulse rate is not materially increased, whereas, the pulse-pressure and total work of the heart are augmented in a considerable measure. The respiratory movements are somewhat hindered, owing to the upward displacement of the diaphragm, but the total interchange of the gases is rather increased. This is made possible by a broadening out of the thorax. A moderate hypertrophy of the thyroid and parathyroid bodies is not uncommon even during normal pregnancy,³ and a similar change may be displayed by the hypophysis and the cortex of the adrenal glands.⁴ Peculiar yellowish discolorations, the so-called chloasmæ, appear in different regions of the skin. The pregnant woman also displays mild mental disturbances which are associated with an increased irritability of the entire nervous system. Thus, she may crave for the most unusual articles of food and suffer from mental depression and all sorts of imaginary evils. For the neuropathic woman, this period is one of danger, because these mild and functional psychoses may finally develop into a permanent or true psychosis.

In general, however, it cannot be doubted that pregnancy improves the condition of the woman, and while this change may not be apparent during the first few months, it certainly makes itself felt later on.⁵ The initial period of fatigue, lassitude and mental depression appears to be associated with the rapid depletion of her energy by the rapidly growing embryo. Later on, however, when a more stable equilibrium has been established by the development of greater storative qualities, her health improves perceptibly. This is especially true of her power of retaining nitrogen and constructing proteid tissue, which in turn leads to an increase in her weight and a decrease in the nitrogenous content of her urine from its previous level of about 90 per cent. to

¹ Opitz, *Zeitschr. für Geburtshilfe und Gynec.*, lxxii, 1913, 351, and Hofbauer, *ibid.*, lxi, 1908, 200.

² Jaschke, *Archiv für Gynec.*, xciii, 1911, 809.

³ Seitz, *Ännere Sekretion und Schwangerschaft*, Leipzig, 1913.

⁴ Mayer, *Archiv für Gynec.*, xc, 1910, 600.

⁵ Bar, *Léçons, de path. obstétricale*, Paris, 1907.

80 or 85 per cent. There may also be noted a slight increase in the percentage of ammonia.

The Development of the Placenta.—The cytoplasm of the ovum contains a certain amount of nutritive material which, however, does not last for a longer time than its initial period of growth. Hence, a new source of supply must be established as soon as the ovum has become firmly attached to the maternal tissues. It will be remembered that the defect through which the ovum has entered the uterine decidua, closes soon afterward, the layer of tissue now investing the ovum externally being known as the decidua reflexa, and that lining the substance of the uterus as the decidua vera. Directly underneath the developing ovum lies the decidua basalis. The latter, together with the enveloping membranes of the ovum, now enters into the formation of a special organ, the placenta, the purpose of which is to effect an interchange of materials between the fetus and the mother. Evidently, this structure arises from a union of certain fetal and maternal tissues, and consists essentially of vascular outgrowths or villi of the chorion of the fetus which become approximated to large blood spaces formed in the decidua basalis of the uterus. Consequently, the blood of the mother does not actually pass into the channels of the fetus, but remains separated from that of the latter by the lining of the blood-vessels and the epithelial layers of the villi of the chorion.

To begin with, this separation is effected by a single layer of cells of the ectoderm and constitutes the external envelope of the blastodermic vesicle. As soon as the ovum has become firmly lodged upon the decidua, these cells proliferate and project outward in the form of minute finger-like processes or villi, which impart a peculiar fringed appearance to this layer. Each villus, therefore, is situated upon a substratum of connective tissue with which it remains connected by a stalk, and consists of an outer epithelial covering and an inner framework of connective tissue. The cells of the former frequently proliferate, forming additional minute buds upon the individual villi. It is also to be noted that the latter are very numerous in that region of the ovum which lies most directly in contact with the basilar decidua.

Mention should also be made of the amnion which, when fully formed, completely invests the embryo, and eventually comes to lie in close contact with the inner surface of the chorion. The amnion is developed as two layers, an external one consisting of mesoderm and an internal one composed of cuboidal or flattened ectoderm. A clear fluid then collects between these layers which gradually increases in quantity as pregnancy progresses. Its average amount at term is 600 c.c. and its specific gravity 1.002 to 1.028. It is derived chiefly from the mother's serum by transudation through the amniotic epithelium,¹ but may also contain fetal urine during the last months of pregnancy if the mother's kidneys become defective.² The function of this fluid is chiefly protective, because it serves to mitigate the force of sudden shocks and to prevent the loss of heat from the fetus by investing its surface with a medium of constant temperature. Secondly, it keeps the developing fetus away from other tissues so that it cannot become adherent to them. Thirdly, it may supply water as well as albumin to its tissues. Lastly, it serves as the normal dilator of the cervix of the uterus during labor. In this case, it acts as a

¹ Ahlfeld, *Zeitschr. für Geb. und Gynec.*, lxi, 1911, 91.

² Wolff, in *Oppenheimer's Handb. der Bioch.*, iii, 1910, 709.

FIG. 538.—DIAGRAMMATIC REPRESENTATION OF RELATIONSHIP OF OVUM TO DECIDUA.

1, In latter half of first week; 2, a few days later; 3, a few months later, when placenta is well defined (Webster): *a*, Fetal mesoblast, showing indications of beginning extension into trophoblast stalks in 1, actual extension in 2 and 3; *b*, trophoblast, being reduced in 3 and constituting here the layer of Langhans; *c*, trophoblast lacuna in 1, enlarged in 2 and 3 as an intervillous space; *d*, syncytium, seen in its earliest stage in 1; *e*, decidua; *f*, maternal blood-sinus; *g*, endothelium lining maternal sinus; *h*, epiblastic covering of cord; *i*, amniotic epiblast; *j*, umbilical vein; *k*, umbilical artery; *l*, amniotic mesoblast; *m*, extension of decidua on under surface of chorion at edge of placenta; *n*, large villus-stem.

rounded bag of water and enables the contracting uterus to bring an equal pressure to bear upon the entire circumference of the cervix, thereby preventing tears.

The Function of the Placenta.—At about the fourth month, this organ consists chiefly of villi of the chorion which contain connective tissue cells and numerous blood-vessels. The cells of the tips of these projections proliferate very actively and finally invade the decidua. The spaces between these projections, as well as those separating the individual villi, are filled with maternal blood, which gains entrance to them through free openings in the maternal blood-vessels. It will be seen, therefore, that the maternal blood remains separated from that of the fetus by the double layer of epithelium of the chorion and the stroma and walls of the blood-vessels of the villi. Consequently, the placenta really represents a mass of maternal blood which has been temporarily diverted into the spaces between the chorionic membrane and the decidua basalis of the uterus. Into this blood project the capillary coils of the different villi, without, however, establishing a direct connection between these two types of blood.

Regarding the manner in which the constituents of one are interchanged for those of the other, nothing further can be said than has already been mentioned when discussing the causes underlying the formation of any secretion. Diffusion and osmosis are augmented by a vital activity of the lining cells of the chorionic villi. Evidently, these cells play the part of a gland. The oxygen and nutritive particles are made to pass into the umbilical vein of the fetus, whereas the waste products of the latter are directed from the capillaries of its two umbilical arteries into the maternal venous system. Fat globules have been observed to traverse the chorionic lining cells and, besides, these cells serve as storehouses of glycogen, from which the fetus may derive extra amounts of sugar whenever in need of them. Attention should also be called to the fact that considerable quantities of glycogen are deposited in the uterine mucosa some time before each menstrual period, a provision of Nature which evidently is made in anticipation of the arrival of a fertilized ovum. Thus, it will be seen that the placenta really represents a combination of organs, because it serves jointly as the respiratory, digestive and excretory mechanisms of the developing young. By analogy it may then be concluded that the fetus really occupies the position of a tissue, its nutrition being cared for as if it were an actual part of the maternal body. Practically any substance contained in the mother's blood may find its way into the fetus.

Within 10 to 20 minutes after the expulsion of the fetus, the placenta is cast off from the uterus, forming what is known as the after-birth. The latter appears as a flat, rounded plate, weighing 500 to 600 grams, and measuring 15 to 18 cm. in diameter and 2 to 3 cm. in thickness. Its outer or maternal surface is rough and presents numerous irregular depressions, or cotyledons, while its inner or fetal surface is covered by amniotic membrane and possesses, therefore,

a smooth and glistening appearance. The umbilical cord, containing the blood-vessels which connect the fetus with the placenta, usually enters near its center. It measures 1.0 to 2.5 cm. in diameter and about 55 cm. in length. Its outer envelope consists of several layers of epithelium which are directly continuous with the skin of the fetus. Its connective tissue reticulum contains a mucoid substance, known as the Whartonian jelly, which serves as a protection to its blood-vessels. The latter ramify extensively directly below the surface of the amnion, so that they are already well subdivided before they reach the chorion.

The Nutrition of the Embryo.—In the earliest stage of its development the embryo possesses no circulatory system, but derives its nutritive material from the media surrounding it. Shortly afterward there is developed the yolk-circulation which, however, does not continue for any length of time, because the supply in this material is very limited. For this reason, its place is taken during the third week by the circulatory mechanism of the chorion which is eventually changed into the complete circulatory system of the placenta. The latter becomes functional at the end of the second month of intra-uterine life, so that the fresh blood henceforth leaves the placenta by way of the umbilical vein, while the impure blood is returned to it by way of the umbilical arteries. The fetal heart beats as a rule at the rate of 120 to 140 in a minute. It may be heard at first directly over the symphysis pubis, and during the later months at a point about midway between the umbilicus and the superior iliac spine, according to the position of the fetus.¹ Actual movements of the fetus are perceived at about the eighteenth or twentieth week.

The oxygen requirement of the fetus is relatively small, because the developing organism is protected against a loss of heat by the mother. This implies that the heat produced in consequence of the oxidations in its tissues is stored, giving rise to a temperature which is usually somewhat higher than that of the mother. As far as the actual transfer of oxygen is concerned, it has been proved that the blood of the umbilical vein is lighter in color than that of the umbilical arteries, and contains oxyhemoglobin. In this connection it might also be mentioned that ether and chloroform, when administered to the mother, are transferred to the fetal blood.

The occurrence of a transfer of nutritive material is proved conclusively by the constant growth of the fetus. In this process the chorionic epithelium plays a part analogous to that of the intestinal wall, *i.e.*, it subjects the nutritive substances to radical changes in order to render them assimilable by the cells of the fetal tissues. This is true of the albuminous material as well as of fats. Both are first reduced into simpler compounds and are then rebuilt into tissue-protein and body fat. In the case of the fat, Hofbauer² has shown that

¹ First heard by Mayor of Geneva, in 1818.

² *Zeitschr. für Geburtsh. und Gynec.*, lxiv, 1909, 668.

whereas fat stained with Sudan-red actually reaches the intervillous spaces, it reappears as unstained globules within the syncytium of the villi. But even the pigment so separated traverses these cells and circulates in the fetal blood. Glycogen is found in all the tissues of the embryo during its period of most active growth, although later on, when the liver becomes functional, it disappears almost completely from the skin, lungs and other organs. In order to effect these reductions and syntheses, the chorionic epithelium must be in possession of different enzymes, an assumption which has more recently found experimental proof in the work of Bergell and Folk,¹ and others. Thus, the especially high requirement of the fetus in salts may bring it about that the bones, and particularly the teeth, of the mother become affected. Some women are more prone to suffer from this partial decalcification than others, a difference which seems to be associated with their varying power of assimilating calcium from their food.

It is also a well-known fact that drugs may be transmitted from the mother to the fetus, as well as in the reverse direction. This is true of potassium cyanid, alcohol, strychnin, and many inorganic and organic salts. Bacteria as such are rarely transferred, so that the placenta may be regarded as playing the part of a filter. This power it loses if diseased. Neither does it seem to be able at any time to exclude toxins.²

Determination of Sex.—In 1897 Schenk made the startling claim that the nutrition of the embryo may be influenced in such a way as to produce either a male or a female offspring. This speculation he based upon the older view which contends that sex is dependent upon the nutritive superiority of the father or mother. The work of Rauber,³ Morgan,⁴ Wilson⁵ and Doncaster,⁶ however, has proved that sex is determined before the beginning of segmentation, *i.e.*, either at the time or immediately after the union of the sperm-cells. The actual factor here concerned seems to be the spermatozoön which may or may not embrace an accessory chromosome. Thus, it has been found that the spermatocytes of many animals contain an odd number of chromosomes, while in the oöcytes they appear in pairs and are arranged in a similar manner. In fact, the spermatocytes are said to appear in three forms, namely: (a) one in which a centrosome remains without a mate, (b) one in which the chromosomes of one pair differ in size, and (c) one in which they are all alike. The reduction in the number of these chromosomes during fertilization must then give rise to three types of spermatozoa, namely: (a) one in which an odd chromosome is present, (b) one in which the number of the chromosomes is even but in which a small or aberrant chromosome is present, and

¹ Münchener med. Wochenschr., 1908.

² Lubarsch, *Ergebn. der allg. Path. und path. Anat.*, 1896.

³ *Überschuss an Knabengeburt und seine biol. Bedeutung*, Leipzig, 1900.

⁴ *Heredity and Sex*, New York, 1913.

⁵ *Jour. of Exp. Zoology*, iii, 1906, and *Science*, 1909.

⁶ *The Determination of Sex*, Cambridge, 1914.

(c) one in which the chromosomes are evenly reduced and identical in appearance. If either one of the first two varieties fertilizes the egg, a male results, whereas that variety which possesses the identical chromosomes gives rise to a female.

In man, the number of the chromosomes is given as 23 and 24 respectively. The first type of spermatozoön gives rise to males and the second to females. Consequently, the segmentation nucleus must contain 47 chromosomes in the first case and 48 in the second. These facts, however, explain sex only and do not show why the number of male children born at full term is greater than that of the females. The ordinary relationship of 106 males to 100 females rises to 130:100 in women whose first children were born after they had reached their thirtieth year, and to 140:100 in women whose first children were born after their fortieth year. The statistics gathered more recently confirm the old view that a greater number of males are born during times of war.

Parturition.—The fetus is fully developed and ready to be expelled 280 days after the first day of the last menstrual period, but this date is only approximate, because normal children are also born as early as 240 and as late as 320 days after the day just specified. In fact, even these extremes are exceeded sometimes. These discrepancies are due in part to differences in the rate of development, and in part to our inability of exactly determining the time of the fertilization of the ovum. Evidently, this calculation cannot be based upon the day of the coitus, because fertilization takes place at variable intervals after insemination. Such differences have also been noted among the domestic animals in which the duration of pregnancy is usually determined in accordance with a single coitus. In the cow, for example, it is estimated at 280 days, with extremes of 240 and 310 days, and in the mare at 366 days, with extremes of 307 and 412 days.

Labor consists essentially in the development of a driving force which is capable of separating the fully formed fetus from the mother without injury to either participant. Particularly at this time the female genitals display their dynamic qualities most advantageously, and this is true especially of the uterine musculature which plays the principal part in this process. Already during pregnancy the woman experiences intermittent contractions of this organ which, however, do not give rise to unpleasant sensations. At the time of labor, these contractions increase in intensity and are associated with a distinct pain which possesses a peculiar bearing down character, *i.e.*, they begin in the sacral region and slowly pass to the abdomen and toward the thighs. To begin with, they recur at intervals of from 15 to 30 minutes, but later on as frequently as every 2 minutes. They may then last for 60 to 90 seconds. The dilatation of the cervix having been accomplished, the climax of these "labor pains" is reached at the time when the head distends the vulva. In many cases, how-

ever, the suffering is very slight and labor is completed almost without pain.

These contractions possess a peristaltic character and may develop a pressure of 30 pounds, the average being 17 pounds; in fact, in rare instances pressures of from 50 to 100 pounds have been encountered. It should not be forgotten, however, that the actual expulsion of the fetus also brings into play the abdominal press which greatly augments the force of the uterine musculature. In addition, the patient braces her body and contracts other muscles to steady herself. The frequency of the heart and the arterial pressure increase during the contractions, whereas the respiratory rate decreases. The process of labor is usually divided into three stages, namely:

(a) From the beginning of the first cramp-like pains to the completion of the dilatation of the cervix; leading to the rupture of a few local blood-vessels and the discharge of the amniotic fluid.

(b) From the rupture of the membranes to the complete delivery of the child.

(c) The placenta separates from the uterine wall and is expelled together with a small quantity of blood (500 c.c.). The uterus gradually recedes, forming a solid tumor well below the umbilicus.

The average duration of labor in primiparæ is 18 hours; 16 hours of this period being consumed by the first, 1 hour and 45 minutes by the second, and 15 minutes by the third stage. It is usually more prolonged in elderly women, but is much shorter in multiparæ. Labour is essentially a reflex process in which the uterine musculature plays the principal part. The correctness of this deduction is proved by the fact that even a uterus the nerves of which have been divided, is capable of successfully expelling its contents. Consequently, we may omit many of the theories which have been formulated to explain the onset of labor and confine ourselves to those which hold that this process is not dependent upon a stimulation of certain nerve centers, but is instigated by a local stimulus either in the form of mechanical impacts or in the form of a hormone contained in the blood stream. In the first instance, the presumption would be that the steadily growing fetus eventually produces a maximal distention of the uterus and thereby incites a contraction of its musculature. But this view does not coincide with the observation that large fetuses are often retained for a much longer time than those of smaller size. Among the chemical theories might be mentioned the one advocated by Brown-Séquard (1853), which states that the contractions of the uterus are incited by a sudden increase in the carbon dioxide content of the mother's blood. This explanation, however, does not clearly depict the cause of this accumulation, nor is it quite certain that ordinary amounts of carbon dioxide could actually produce this result. More plausible are those theories which localize the stimulus in the fetus itself. Thus, Spiegelberg has stated that certain of its excretory substances eventually fail to be eliminated and attack the uterus directly. This view finds

substantiation in the experiments of Kruiger and Offergeld,¹ which prove that even the denervated uterus may show a normal onset of labor. In addition, Sauerbruck and Heide² have demonstrated that artificially united female rats (symbiosis) may influence one another. Thus, it was noted that the onset of the uterine contractions in one invariably produced these contractions in the other animal. If, however, the other was not pregnant, it then showed certain symptoms indicative of a serious illness. Eden³ and Williams⁴ have called attention to the fact that the placenta undergoes senile changes at term which increasingly interfere with the nutrition of the fetus. The accumulation of the waste products resulting in consequence of this condition, undoubtedly evokes local stimuli which diminish the output of nitrogen, and depress the general processes of oxidation. Consequently, we are forced to conclude that labour is under the direct control of a local mechanism which may be activated either chemically or mechanically. The central nervous system, on the other hand, serves merely as a regulating and correlating agent. It is a well-known fact that emotions and other sensory impressions may influence the onset and progress of labor as decidedly as the activated uterus may alter the functional state of other organs.

¹ Archiv für Gynec., lxxxiii, 1907, 257.

² Münchener med., Wochenschr., 1910.

³ Jour. of Path. and Bact., 1897.

⁴ Jour. of Obst., xli, 1910.

INDEX

- ABDOMINAL press**, 479, 531
 in labor, 1145
 in micturition, 1077
 in vomiting, 1011
 reflex, 598
 type of respiration, 466
Abducens nerve, 650
Aberration, chromatic, 815
 spherical, 815
Ablation of cerebellum, 711
 of motor area, effects of, 679
Absorption bands of spectrum, 192
 from cavities of body, 1033
 from intestinal canal, 1027
 of carbohydrates, 1029
 of fats, 1030
 mechanistic theory, 1031
 chemical theory, 1031
 of proteins, 1031
 of water, 1027
 through skin, 1034
Acapnia, 521, 523
Acceleration, heart, 309
Accelerator nerve fibers of heart, 311
Accessory nerve, 655
Accommodation in various animals, 820
 of human eye, 822
 normal, limit of, 828
 proofs, 823
 range, 828
 reflex, 648, 812, 814
Acetone in urine, 1086
Achillis jerk, 599
Achlorhydria, 923
Achromatic lenses, Dolland's, 816
Achromatism, 816
Achromatopsia, 888
Achroë-dextrin, 993
Acid, cholalic, 947
 cholic, 947
 glycocholic, 947
 hematin, spectrum of, 195
 hippuric, in urine, 1087
 hydrochloric, 952
 sarcolactic, 1041
 taurocholic, 947
Acidophiles, 199
Acidosis, 1043, 1086
Acini of glands, 892
Acromegaly, 979
Action, reflex, 109
Activator, 990
Active immunity, 246
Acuity, tactile, 736
 visual, 838
Adaptation of sense organs, 732
Addison's disease, 969
Adenoid, 907
Adiadochokinesis from cerebellar disease, 713
Adrenal glands, 967
 function, 970
 innervation, 973
 position, 967
 removal, 969
 structure, 967
Adrenalin, 952, 971
 effect on circulation, 971
 on eye, 975
 on metabolism, 975
 on muscle tissue, 975
 on salivary secretion, 916
Adrenalin-glycosuria, 975
Adrenalin-hyperglycemia, 975
Adrenin, 971
 effects on circulation, 971
Absorption, 1027
Ærobes, 445
Ærotonometer, 490
 Bohr's, 491
Afferent nerve fibers of heart, 324
 neuron, 109
After-birth, 1141
After-images, negative, 882
 positive, 882
Age, effect of, on arterial blood pressure, 370
 on metabolism, 1054
 on respiratory quotient, 516
Agglutinins, 248
Agnosia, auditory, 697
 tactile, 684, 697
 visual, 697
Agraphia, 690, 695, 696, 698
Air calorimeter, 1090
 complemental, 480
 composition of, effect on respiratory quotient, 516
 expired, character of, 486
 inspired, character of, 486
 minimal, 481
 residual, 480
 respired, quantitative determination, 479
 stationary, 481
 supplemental, 480
 tidal, 480
 and blood, interchange of gases between, 488
 chemical theory, 488, 494
 physical theory, 489

- Air-bladder of fish, 450
 Air-cells of lung, 451
 Albuminuria, 1074
 Alcohol, effect of, on speed of nerve conduction, 133
 Alcoholic fermentation of milk, 901
 stimulants, 1063
 Alexia, 696
 Alexin, 250
 Alimentary canal, absorption of reduced foodstuffs from, 1022
 length of, in various animals, 999
 muscles of, 1000
 of birds, 998
 of mammals, 998
 glycosuria, 966, 1043
 Alteration theory of electrical current of injury, 104
 Alternating reflexes, 592
 Altman's theory of structure of protoplasm, 24
 Alveolar theory of structure of protoplasm, 24
 Alveoli, 452
 of lungs, 451
 Amaurosis, 887
 Amblyopia, 887
 Amboceptor, 251
 Ambrosial odors, 747
 Ameboid movement, 38
 Ametropia, 855
 Amino-acids in urine, 1087
 Amino-nitrogen, 1051
 Amitosis, 1109, 1110
 Ammonia, 1051
 in urine, 1086
 Amnion, 1140
 Amniotic fluid, 1140
 Amœba, 20
 Amphibian heart, 256
 lung, 451
 Ampulla, hair-cells of, activation of, 791
 Amusia, 698
 Amylase, 513, 935
 Amyolytic action of pancreatic juice, 996
 enzymes, 989
 Amylopsin, 935, 996
 Anabolism, 985
 Anaerotic limb of arterial pulse, 383
 Anaërobes, 445
 Anaphase of mitosis of cell, 1111
 Anaphylactin, 252
 Anaphylaxis, 251
 to apomorphin, 252
 to cocaine, 252
 Anarthria, 695
 Anelectrotonus, 143, 145
 Anemia, pernicious, 905
 theory of sleep, 723
 Anencephalus, 671
 Anesthesia, constriction of pupil in, 814
 Anesthetics, effect of, on speed of nerve conduction, 133
 Anestrus, 1133
 Angiometer, Hürthle, 383
 Animal electricity, 99
 heat, 1089
 reflex, 584
 Animalculists, 1117
 Animals, anosmatics, 690
 arterial blood-pressure in, 364
 circulatory system in, 254
 homoiothermal, 1093
 macrosmatic, 690
 microsmatic, 690
 osmatic, 690
 poikilothermal, 1093
 process of accommodation in, 820
 Animate material, 19
 Ankle-clonus, 75, 592
 Annuli fibrosi, 264
 Anode, 58
 Anosmatic animals, 690
 Anoxemia, 521
 Antagonistic reflexes, 592
 Anterolateral tract, superficial, 618
 Antibodies, 247
 Anti-enzyme, 992
 Antigens, 247
 Antiperistaltic wave, 1014
 Antithrombin, 214
 Antitoxic sera, 246
 Antitoxin, diphtheria, 246
 Antrum, mastoid, 764
 pylori, 1006
 Anvil bone of ear, 766
 Aorta, 254
 Aortic vestibule, 267
 Apex beat, location, 282
 Aphakia, 830
 Aphasia, 693
 motor, 694
 sensory, 696
 Aphemia, 695
 Apnea, 522
 fetalis, 523
 spuria, 523
 vagi, 523
 vera, 523
 Apomorphin, anaphylaxis to, 252
 Apoplexy, 230
 Appetite, 752
 Appetizers, effect of, on gastric juice, 930
 Apraxia, 695
 Aqueous humor, 809
 Arachnoid, 716
 Arbor vitæ, 707
 Archipallium, 665
 Area, body-sense, 681
 frontal association, 699
 motor, of cerebrum, 671
 location, 673
 Areas, touch, 739
 Argyll-Robertson sign, 813
 Aristotle's four mundane elements, 794
 Aromatic odors, 747
 Arterial blood pressure. See *Blood pressure, arterial*.

- Arterial pulse, 377
 - cause, 377
 - frequency, 379
 - percussion-wave, 384
 - registration of, 381
 - wave, anacrotic limb, 383
 - apex, 384
 - catacrotic limb, 384
 - character, 383
 - dicrotic, 384
 - notch, 384
 - postdicrotic, 384
 - predicrotic, 384
- Arteries, 254
- Arterioles, 254
- Artery, umbilical, 260
- Articulation, positions of, 55
- Artificial respiration, 482. See *Respiration, artificial*.
- Aryepiglottic folds, 544
- Arytenoid cartilages, 542
 - muscle, 547
- Asphyxia, 525
 - color of blood in, 161
- Assimilation leukocytosis, 201
 - phenomenon of, 31
- Association area, frontal, 699
 - reflexes, 582, 592
 - system of cerebrum, 661
 - visual, 686
- Astasia from cerebellar disease, 713
- Astereognosis, 684
- Asthenia from cerebellar disease, 713
- Astigmatism, 855
 - against the rule, 856
 - irregular, 856
 - regular, 856
 - with the rule, 856
- Asynergia from cerebellar disease, 712
- Ataxia from cerebellar disease, 713
- Atmosphere, 446
- Atonia from cerebellar disease, 713
- Atropin, effect of, on inhibitor reaction of heart, 317
 - on salivary secretion, 916
- Aubert and Forster's perimeter, 851
- Auditory agnosia, 697
 - center, 689
 - fatigue, 780
 - meatus, 763
 - external, 764
 - nerve, 651
 - radiation, 661
- Auricle, auditory, 763
- Auricles of heart, 255
 - discharging period, 307
 - filling, in intra-auricular pressure, 299
 - function, 297
 - longitudinal layer, 265
 - musculature of, 265
 - structure, 263
 - transverse layer, 265
- Auricular complex of electrocardiogram, 288
- Auricular fibrillation, 279
 - systole, position of heart valves in, 307
- Auriculoventricular bundle, 264
 - valves, 268
- Auscultation method of recording arterial blood pressure, 368
- Autacoid substances, 952
- Autonomic nervous system, 627. See *Nervous system, autonomic*.
- Avalanche conduction, 769
- Axis-cylinder, 111, 113
 - function, 116
- Axon, 108, 111
- Axon-reflexes, 637
- BABINSKI phenomenon, 599
- Bacteria, intestinal, reaction of, on carbohydrates, 997
 - on fats, 997
 - on proteins, 998
- Bacteriolysins, 248
- Bacteriolysis, 248
- Bahnung, 573
- Banting's cure for obesity, 1056
- Barcroft's blood-gas apparatus, 501
 - modification of Töpler's pump for extraction of gases from blood, 499
- Barometric pressure of gases, changes in, 519
- Bartholin's duct, 909
 - glands, 1136
- Basal ganglia, 703
 - heat production, 1104
 - membrane, 775
- Basedow's disease, 959
- Basilar membrane, 772
- Basket cells, 707
- Basophiles, 199
- Bathmotropic cardiomotor impulses, 315
- Baths, effect of, on body temperature, 1098
- Bell-Magendie law, 620
- Bends, 522
- Beri-beri, cause, 927
- Bernstein's experiment on heart beat, 334
- Bert's experiment proving centripetal nerve conduction, 128
- Betz, cells of, 613
- Biconcave lens, 800
 - refraction by, 803
- Biconvex lens, conjugate foci, 801
 - optical center, 800
 - principal axis, 800
 - focal distance, 801
 - refraction by, 800
 - secondary axis, 800
- Bidder's ganglion, 318, 332
- Bile, 938, 939
 - characteristics, 940
 - circulation, 947
 - formation, 943
 - function, 996

- Bile, phospholipins, 948
 pigments, 948
 resorption, 944
 special constituents, 947
 storage, 941
 Bilicyanin, blue, 948
 Bilirubin, 948
 Biliverdin, 948
 Bimolecular reaction, 992
 Binocular vision, 869, 872
 Biot's respiration, 524
 Biplegia, 679
 Birds, alimentary canal of, 998
 heart of, 258
 lungs of, 451
 Bismuth α -ray study of stomach, 1008
 Bladder, urinary, 1076
 nervous control, 1077
 Blastula, 1119
 Blepharospasm, 592
 Blind spot, 834
 demonstration of, 835
 form of, 836
 Blindness, blue-, 888
 color-, 887
 green, 888
 psychic, 688
 red-, 888
 word-, 688, 696
 Block, heart-, 278
 Blood, 157
 absorption of gases by, 497
 and tidal air, interchange of gases
 between, 488
 chemical theory, 494
 physical theory, 489
 and tissues, interchange of gases be-
 tween, 496
 as protective mechanism, 245
 carbon dioxide in, condition of, 505
 chemical composition, 168
 cholesterin in, 169
 circulating, total quantity, 357
 circulation of, 253, 347. See also
 Circulation.
 coagulation of, 211. See also *Coagu-*
 lation of blood.
 color, 160
 corpuscles, blood plasma and, relative
 amount, 159
 determining amount, direct
 method, 159
 indirect method, 160
 red, 172
 chemical properties, 181
 color, 172
 composition, 181
 disintegration of, 198
 duration of life, 197
 hemoglobin and stroma of, sepa-
 ration, 181
 increase at high altitudes, 179
 life history, 195
 number, 176
 physical characteristics, 172
 Blood corpuscles, red, shadows, 181
 shape, 172
 size, 174
 stroma of, constituents, 183
 variations in number, 178
 in shape, 175
 white, 199
 allied functions, 207
 chemical composition, 201
 classifications, 199
 color, 199
 contractility, 202
 dualistic origin, 202
 fate, 202
 formation of, in spleen, 904
 monophyletic origin, 202
 motion, 202
 number, 200
 origin, 202
 physical properties, 199
 shape, 199
 size, 199
 decalcification of, effect on coagula-
 tion, 223
 defibrination, 226
 description, 159
 distribution, 226, 228
 dog's, composition, 168
 dust, 159
 electrical conductivity, 165
 extraction of gases from, 497
 flow, 394
 friction of, 166
 gaseous composition, 522
 general characteristics, 157
 greater circuit, 259
 horse's, composition, 168
 in asphyxia, 161
 infusion of, 230
 laked, 181
 lecithin in, 169
 loss of, 226, 230
 menstrual, coagulability of, 226
 methods of collecting, 221
 of determining quantity of, 226
 nitrogen in, condition of, 507
 odor, 162
 osmotic pressure, 164
 oxygen in, condition of, 502
 plasma, 159
 and corpuscles, relative amount,
 159
 constituents, 170
 salted, 223
 plasma-poor, 180
 platelets, 159, 207, 208, 214
 fate, 208
 methods of examination, 208
 origin, 208
 physical characteristics, 207
 policemen, 204
 pressure, 354
 arterial, auscultation method of
 recording, 368
 cardiac variations, 377

- Blood pressure, arterial, effect of age
 on, 370
 of change of position on, 372
 of deep breathing on, 371
 of eating on, 371
 of labor on, 371
 of menstruation on, 371
 of muscular exercise on, 371
 of pregnancy on, 371
 of sleep on, 370
 factors influencing, 370
 graphic method of recording, 368
 in animals, 364
 in various arteries, 364, 366
 methods of determining, 362
 recording, Crampton's index of
 conditions in, 372
 direct method, 362
 indirect method, 362, 366
 palpation method, 366
 variations in, 365
 causes, 391
 pulsatory, 377
 respiratory, 390, 486
 capillary, 376
 venous, 373
 indirect method of recording, 374
 negative, area of, 374
 variations in, cardiac, 388
 respiratory, 390
 causes, 391
 reactions of, 164, 248
 residual, 229
 serum, 171, 212
 sodium chlorid in, 169
 specific gravity, 162
 velocity, 402
 determination of, 404
 chemical method, 397
 direct method, 394
 indirect method, 397
 stream, volume, 394
 measuring of, calorimetric
 method, 397
 sugar content, 169
 supply, cerebral, regulation of, 443
 taste, 162
 temperature, 162
 total quantity, 226
 transfusion of, 230
 urea content, 170
 viscosity of, 166
 whole, composition, 167
 Blood-vessels, elasticity of, 358
 innervation of, 411
 nervous regulation of, 411
 Blue-blindness, 888
 Bodies, opaque, 795
 purin, 1051
 tigroid, 563, 564
 translucent, 795
 Body cavities, absorption from, 1033
 ciliary, 819
 different regions, temperature of,
 1094
 Body fat, source of, 1044
 history of foodstuffs in, 1037
 metabolic requirements, 1052
 proteins, source of, 1048
 sugar supply of, regulation, 1042
 temperature, 1093
 effect of baths on, 1098
 of clothes on, 1101
 of nervous depressants on, 1106
 of varnishing skin on, 1105
 factors varying, 1095
 in various regions, 1094
 regulation of, 1097
 rise of, after death, 1105
 voluntary factors controlling, 1101
 Body-sense area, 681
 localization, 681
 Bohr's aërotonometer, 491
 Bolometer, resistance, 1099
 Bolus, food, 1001
 Bone-marrow, myeloplaxes, 207
 Bones, cranial, conduction of sound
 waves by, 779
 ear, 764, 766
 movements, 767
 Bornstein's chemical method of meas-
 uring volume of blood stream, 401
 Botulism, 1035
 Boyle's law, 1025
 Brain, growth, 717
 human, convolutions of, 667
 weight of, 666, 718
 Brain-sand, 981
 Breasts. See *Mammary glands*.
 Breathing, deep, effect on arterial blood
 pressure, 371
 Brewster's stereoscope, 876
 Brightness, 880
 Brodie recorder, 399
 Brodie and Russell's method of esti-
 mating coagulation time of blood, 219
 Bronchi, 451, 452
 Bronchial capacity, 481
 murmur, 477
 Bronchiolar tubules, 451
 Bronchioles, 451, 452
 Brownian molecular motion, 37
 Brown-Séquard's inhibition theory of
 sleep, 723
 Bruit de souffle, 368
 Buds, lateral, 108
 Buffy coat, 212
 Bulb, olfactory, 644
 Bulbocavernosus muscle, 1127
 reflex, 599
 Bulbospiral fibers of ventricles, 266
 Bundle, anterior ground, 613
 tectospinal, 616
 Held's, 616
 lateral ground, 613
 Lissauer's, 616
 Monakow's, 616
 of Helweg, 616
 of His, 264
 septomarginal, 616

- Burdach, column of, 613
 Burning odors, 747
 Burton-Opitz's apparatus for measuring volume of blood stream, 395
 Bush-tea, 1063
 Bütschli's theory of structure of protoplasm, 24
 Butter, 900
 Butyrin of milk, 902

 CACHEXIA thyreopriva, 957, 962
 Caffeine, 1062
 Caisson disease, 522
 Calcium rigor, 337
 Calliano's method of artificial respiration, 483
 Calorie, 1091
 Calorimeter, 1090
 air, 1090
 micro-, of Hill, 1092
 respiration, 1091
 water, 1090
 Calorimetric method of measuring volume of blood stream, 397
 Calorimetry, 1089
 Canal, membranous, of cochlea, 775
 of Schlemm, 805
 osseous, of cochlea, 772
 Canaliculus lacrymalis, 808
 Canals, semicircular, 771, 785
 Cannon and Mendenhall's graphic coagulometer, 220
 Capillaries, 254
 contractility of, 416
 endothelial lining cells of, 207
 Capillary blood pressure, 376
 electrometer, Lippmann's, 101
 Caproic odors, 747
 Caproin of milk, 902
 Caprylin of milk, 902
 Capsule of Tenon, 804, 869
 Capsules, suprarenal, 967. See also *Adrenal glands*.
 Caput cornu posterioris, 605
 Carbamid in urine, 1083
 Carbohydrate-fat, 1041
 Carbohydrates, 26
 absorption of, 1029
 metabolism of, 1038
 of milk, 902
 of muscle, 86
 reaction of intestinal bacteria on, 997
 Carbon dioxide, effect of, on speed of nerve conduction, 133
 in blood, condition of, 505
 in starvation, 1053
 production of, by muscle, 88
 slight increase in partial pressure, effect on respiratory quotient, 518
 monoxid, affinity of hemoglobin for, 187
 hemoglobin, spectrum of, 194
 Carbonates in urine, 1082

 Cardiac muscle, 42
 tissue, 46
 recess of stomach, 1006
 Cardiogram, 284, 285
 Cardiograph, 284
 Cardiometer, 304
 Johannson and Tigerstedt, 304
 Roy's, 303
 Cardiomotor fibers, 310
 Cardio-pneumatic phenomenon, 1105
 Cardiosensory fibers, 324
 Carnitin, 87
 Carnosin, 87
 Cartilages of larynx, 541
 Caruncula lacrymalis, 808
 Caseinogen, 902
 Castration, effect of, on animals, 982
 on human beings, 983
 Catabolism, 985
 Catacrotic limb of arterial pulse wave, 384
 Catalase, 513
 Catalysis, 987
 Cataract, 830
 Catelectrotonus, 143, 145
 Cathode, 58
 Caustics, 815
 Celiac axis, 433
 Cells, 21
 basket, 707
 carbohydrates of, 26
 central or chief, of gastric glands, 920
 cerebrosids of, 26
 chemical energy, 32
 chemistry, 25
 cholesterin of, 26
 constituents, 25
 cytochrome, 564
 cytoplasm of, 23
 Daniell, 57
 diagram, 57
 demilune, 909
 devouring, 204
 diagram, 25
 endothelial lining of capillaries, 207
 energetics, 32
 fatty acids of, 26
 fiber, of Retzius, 786
 first, origin of, 20
 form, 22
 functional relation of cytoplasm and nucleus, 27
 germ, 1114
 giant, 207
 hair, of ear, 776, 777
 inorganic substances in, 26
 lipoids, 25
 mast-, 200
 mastoid, 764
 metabolism, 29, 30
 movement by changes in turgor, 37
 by swelling of walls, 37
 neutral fat, 26
 nuclein of, 26
 nucleoproteids of, 26, 29

Cells, nucleus, 24
 formation, 24
 of Betz, 613
 of Deiters, 776
 of Golgi, 607
 of Leydig, interstitial, function, 984
 of Purkinje, 560, 708
 olfactory, power of reaction, 744, 745
 phosphatids of, 25
 proteins of, 26
 protoplasm of, 21
 pseudonucleoli, 25
 pyramidal, 560
 size, 22
 somachrome, 564
 somatic, 1114
 sperm-, 1117
 stellate, of Kupffer, 939
 structure, 22
 water of, 26
 Cell-division, direct, 1109
 indirect, 1111
 simple, 1110
 Cell-globulin, 222
 Center, 111
 auditory, 689
 coughing, 641
 defecation, reflex, 1019
 deglutition, 641
 diabetic, 1042
 for closure of eyelids, 641
 for secretion of saliva, 641
 geometrical, of spherical mirror, 796
 glycogenic, 1042
 hearing, 689
 mastication, 641
 micturition, reflex, 1077
 of curvature of spherical mirror, 796
 olfactory, 644, 690
 sight, 684
 smell, 690
 sneezing, 641
 speech, 691, 693
 spinal, for ejaculations, 596
 for erection, 596
 sucking, 641
 taste, 690, 691
 visual, connection with other centers, 687
 vomiting, 641, 1012
 Centers, heat-accelerator, 1102
 heat-inhibitory, 1102
 spinal cord, 596
 Centrum anospinale, 596
 vesicospinale, 596
 Cerebellar localization, 713
 peduncle, superior, 661
 Cerebellum, 706
 ablation of, 711
 arbor vitæ, 707
 asynergia from disease of, 712
 connections, 709
 convolutions, 707
 function, 714
 inferior vermis, 706

Cerebellum, lobuli complicati, 706
 lobulus medianus posterior, 706
 simplex, 706
 lobus quadratus anterior, 706
 median lobe or vermis, 706
 middle peduncle of, 709
 monticulus, 706
 moss fibers of, 708
 roof ganglia of, 708
 structure, 706
 sulcus primarius, 706
 superior peduncle, 709
 vermis, 706
 tendrill fibers of, 708
 Cerebral blood supply, regulation of, 443
 circulation, 440
 cortex, functional separation, 671
 localization, 671, 681
 reflex inhibition, 588
 Cerebrosides, 26
 Cerebrospinal fluid, 236, 718
 function, 721
 system, autonomic system and, connections between, 631
 Cerebrum, 657
 anterior commissure of, 662
 association system, 661
 commissural system of, 661
 comparative physiology, 664
 general function, 657
 gray matter of, general arrangement, 657
 inherited absence of, 671
 mode of development, 662
 motor area of, 671, 673
 projection system, 660
 removal of, 668
 tracts of, classification, 659
 white matter, general arrangement, 658
 Cerumen, 764, 895
 Cervical sympathetic nerve, vasomotor reaction of, 422
 system, 631
 Chalones, 952
 Chauveau unipolar method of nerve and muscle stimulation, 151
 effects of, 154
 Chauveau and Lortet's hemotachometer, 405
 Chemical energy, 729
 imprint theory of light stimulation of retina, 840
 rays, 880
 stimuli, 33
 theories of sleep, 723
 theory of fat absorption, 1031
 of secretion, 892
 Chemicals, effect of, on muscle contraction, 79
 Chemistry of muscle fatigue, 89
 Chest voice, 551
 Chest-register, 553

- Cheyne-Stokes respiration, 523
 Chillarducci's reaction at a distance, 156
 Chloasmæ, 1139
 Chlorhematin, 188
 Chlorids in urine, 1081
 Chloroeruoirin, 160
 Cholagogues, 944
 Cholic acid, 947
 Cholemia, 944
 Cholesterin, 26
 in blood, 169
 of nerve, 114
 Cholesterol, 947
 Cholic acid, 947
 Chorda tympani, 912
 Chordæ tendinæ, 267, 269
 Chorion, 1140
 Choroid, 806
 Chromatic aberration, 815
 Chronometric method of determining hemoglobin, 190
 Chronotropic cardiomotor impulses, 315
 Churning, haustral, 1019
 Chyle, 158, 234, 235
 Chyme, 1009
 Chymosin, 925
 Cilia, 39
 Ciliary body, 806, 819
 ligaments, 806
 movement, 39
 muscle, 806
 innervation of, 830
 Cingulum, 661
 Circuit, primary, 62
 secondary, 62
 Circular fibers of ventricles, 267
 Circulating blood, total quantity, 357
 protein, 1048
 Circulation, 253, 347
 action of epinephrin on, 971
 analogous features, 352
 cerebral, 440
 coronary, 427, 430
 effects of adrenalin on, 971
 of adrenin on, 972
 Harvey's discovery of, 18
 mechanics, 347
 of bile, 947
 peripheral resistance to, 361
 physical consideration, 347
 portal, 433
 pulmonary, 430
 renal, 433
 time required for, 409
 under microscope, 408
 Circulatory system, comparative study, 253
 coronary circuit of, 259
 development, 158
 during fetal life, 260, 261
 greater circuit of, 259
 lesser circuit of, 260
 of fish, 256
 of lower animals, 254
 Circulatory system of mammals, 258
 of sponges, 254
 of vermes, 255
 of vertebrates, 255
 portal circuit of, 259
 pulmonary circuit of, 260
 systemic circuit of, 259
 Circumvallate papillæ of tongue, 748
 Clarke's vesicular column of cells, 607
 Clausius' and Schönbein's ozone-autozone theory of activation of oxygen, 511
 Cleavage nucleus, 1119
 Clonic contracture of muscle, 75
 reflexes, 592
 Clonus, ankle, 592
 Clothes, effect of, on body temperature, 1101
 Clotting of blood, 211. See also *Coagulation of blood*.
 Coagulability of menstrual blood, 226
 Coagulating enzymes, 989
 Coagulation of blood, 211
 chemical changes in, 212
 conditions influencing time, 221
 effect of admixture of neutral salts on, 223
 of decalcification on, 223
 of hirudin on, 225
 of peptonization on, 224
 of snake poisons on, 225
 of substances derived from tissues on, 222
 of temperature on, 221
 extravascular, 211
 intravascular, 217
 physical changes in, 211
 time required for, 219
 of milk, 901
 Coagulation-rigor of muscle, 93
 Coagulins, 222, 248
 Coagulometer of Cannon and Mendenhall, 220
 Coagulum of blood, 211
 Coat, buffy, 212
 Cocain, anaphylaxis to, 252
 Cochlea, 771
 membranous canal of, 775
 osseous canal of, 772
 Cœlenterates, circulatory system of, 254
 Coffee, 1063
 Coil, induction, 62
 Cola, 1063
 Cold spots of skin, 742
 Collapse of lung, 457
 Colloid goiter, 961
 Color contrast, 882
 fusion, 880
 saturation of, 880
 sensibility of retina, 884
 vision, 879
 Hering theory of, 886
 Ladd-Franklin theory, 887
 theories of, 885
 Young-Helmholtz theory, 886

- Color-blindness, 887
 Holmgren's tests for, 888
 Color-wheel of Maxwell, 880
 Colors, complementary, 880
 Colostrum, 900
 corpuscles, 898
 Column, Türck's, 612
 of Burdach, 613
 of Flechsig, 613
 of Goll, 613
 Columnæ carneæ, 267
 Comma tract of Schultze, 616
 Commissural system of cerebrum, 661
 Commissure, anterior, of cerebrum, 662
 hippocampal, 662
 Commutator, Pohl's, 61
 Compensation method of detecting
 electric variations of muscle, 102
 Compensatory pause in heart beat, 343
 Complement, 251
 Complementary air, 480
 Complementary colors, 880
 Complementophile, 251
 Complex lung, 451
 reflexes, 592
 Compression-paralysis of nerve, 131
 Concavo-convex lens, 800
 Conception, 1132
 Concha, 763
 Condiments in diet, 1062
 Conduction, avalanche, 769
 nerve. See *Nerve conduction*.
 Conductivity, electrical, of blood, 165
 of nerve, 124
 irritability and, differentiation, 124
 of protoplasm, 35
 Cone-granules of retina, 832
 Conjugation, 1111
 Conjunctiva, 807
 Conjunctival sac, 807
 Consonants, sound production of, 554
 Constant current, 62
 Consumption, luxus, 1057
 Contractility of protoplasm, 35
 Contraction of muscle, 48. See also
 Muscle contraction.
 of degenerated human muscle and
 nerve, law of, 155
 of normal human nerve and muscle,
 law of, 150
 period of muscular movement, 43
 Pfüger's law of, 146, 148, 149
 wave of muscle, 68
 Contracture of muscle, 74
 clonic, 75
 tonic, 75
 Contralateral effects of hemisection of
 spinal cord, 626
 Conus arteriosus, 256, 267
 Convolutions of cerebellum, 707
 Cooking, proper, value of, 1061
 Coppie's anemia theory of sleep, 723
 Copulation, 1127
 Cord, umbilical, 1142
 Cords, vocal, 550
 Core-conductor, Hermann's, 133
 Cornea, 805, 809
 anterior homogeneous lamella of, 805
 posterior homogeneous lamella of, 805
 refractive power, 809
 Corniculæ laryngis, 542
 Coronary circuit of circulatory system,
 259
 circulation, 427
 Corpora Arantii, 272
 fibrosa or albicantia, 1131
 quadrigenina, 704
 Corpus callosum, 661, 701
 luteum, 1131
 false, 1131
 true, 1131
 striatum, 703
 Corpuscles, colostrum, 898
 Golgi-Mazzoni, 734
 Krause's, 735, 736
 Malpighian, 904
 of Grandry and Merkel, 735
 of Herbst, 735
 of Meissner, 734
 pus-, 201
 red, 172. See also *Blood corpuscles*,
 red.
 salivary, 910
 white, 199. See also *Blood corpuscles*,
 white.
 Corpuscular theory of light, 794
 Cortex, cerebral, functional separation,
 671
 Cortical function, dynamic theory, 701
 Corti's organ, activation, 777
 function, 777
 structure, 775
 rods, 776
 tunnel, 776
 Costal type of respiration, 466
 Coughing, 482
 center for, 641
 Cowper's glands, 1126
 Crampton's index of condition in re-
 cording blood pressure, 372
 muscle, 822
 Cranial bones, conduction of sound
 waves by, 779
 nerves, 640, 642
 functional system of, 642
 system, 631
 Craniotomy, Gall's system of, 672
 Cream, 900
 Creatin, 87, 1051
 in urine, 1087
 Creatinin, 87, 1051
 in urine, 1087
 Cremaster muscle, 1123
 Cremasteric reflex, 592, 598
 Crescents of Gianuzzi, 909
 Cretinism, 957
 Crico-arytenoid muscle, lateral, 547
 posterior, 547
 Cricoid cartilage, 542
 Crista acustica, 785

- Croaking reflex of frog, 588
 Crusta inflammatoria, 212
 Crying, 482
 Crypts of faucial tonsils, 906
 of Lieberkühn, 908, 949
 Crystalline lens, 820
 changes in shape and refractive
 power, 827
 wabbling of, 826
 Crystals, hemoglobin, 184
 Cuneiform cartilages, 543
 Cuorin, 86
 Curd, 901
 Curvature of spherical mirror, center
 of, 796
 Cushny's modern theory of urinary
 secretion, 1072
 Cutaneous receptors, structure, 734
 secretions, 889
 Cuticle, 893
 Cutis vera, 893
 Cybulski's photo-hemotachometer, 405
 Cycle, cardiac, 272
 Cytochrome cells, 564
 Cytoeum, 215
 Cytolysins, 248
 Cytolysis, 248
 Cytophile, 251
 Cytoplasm, 23
 formed elements, 23
 of cell, nucleus and functional rela-
 tion, 27
 DALTON's law of pressures, 497
 Daniell cell, 57
 Dartos, 1123
 Darwin's theory of evolution, 1121
 Deafness, mind-, 688
 word-, 688, 689
 Deamination of ferments, 990
 Death, reflex cardiac, 326
 rise of body temperature after, 1105
 Decalcification of blood, effect of, on
 coagulation, 223
 Decarboxylation of ferments, 990
 Decidua basalis, 1140
 reflexa, 1140
 vera, 1140
 Defecation, 1019
 reflex center for, 1019
 spinal center for, 596
 Defibrination of blood, 226
 Deficiency diseases, 927
 Degeneration, fatty, 1047
 of nerve, 117 See *Nerve degenera-
 tion*.
 Wallerian law of, 621
 Deglutition, 998, 1001
 center for, 641
 function of esophagus in, 1002
 mechanism of, 1002
 nervous control, 1004
 Deiters' cells, 776
 Delirium cordis, 279
 Demilune cells, 909
 Dendrites, 108, 560
 Dental germ, 1001
 special, 1001
 sac, 1001
 sounds, 554
 Depression, fatigue of, 571
 Depressor nerve, 325, 329
 vasomotor reaction, 427
 Deprez-d'Arsonval galvanometer, 99
 Dermis, 893
 Detention theory of accommodation of
 eye, 822
 Deuterocephalon of crayfish, 580
 Deuteroplasm, 1130
 Diabetes mellitus, 965
 Diabetic center, 1042
 Dialyser, 1024
 Dialysis, 1024
 Diaminizing enzymes, 989
 Diapedesis of leukocytes, 206
 Diaphragm, 454
 function of, in respiratory cycle, 462
 Diaphragmatic type of respiration, 466
 Diaschisis effect of Monakow, 701
 Diastase, 513
 Diastole as period of assimilation, 341
 Diastolic pressure, intracardiac, 296
 Diathesis, exudative, 1051
 Diencephalon, 664
 Diet, flavors and condiments in, 1062
 inorganic salts in, 1061
 of man, normal, 1058
 stimulants in, 1062
 value of proper cooking, 1062
 Diffusion, 1023
 of gases, 446
 of proteins, 1026
 pressure, 446
 Digestion, 985
 chemistry of, 985
 leukocytosis, 201
 mechanics of, 998
 Digestive secretions, 908, 918, 938
 Dilatation of heart, 345
 Dimethyl xanthin, 1062
 Diphtheria antitoxin, 246
 Diplopia, 873
 heteronymous, 872
 homonymous, 872
 Direct blood transfusion, 231
 vision, 837
 Disaccharides, 987
 Discrimination, tactile, 625, 736
 Discus proligerus, 1129
 Dismetry from cerebellar disease, 713
 Dissimilation, phenomena of, 31
 Diuresis, 1073
 Diuretics, 1071
 Diver's palsy, 522
 Dog blood, composition, 168
 talking, 692
 Dolland's achromatic lenses, 816
 Dromotropic cardiomotor impulses, 315
 Drugs, action of, on salivary secretion,
 916

- Drugs constricting pupil, 814
 - dilating pupil, 814
 - effect of, on muscle contraction, 79
- DuBois-Reymond's experiment in
 - double nerve conduction, 126
 - induction coil, 62
 - inductorium, 63
 - key for making and breaking current, 60
 - molecular theory of electrical current of injury, 104
- Duct, Bartholin's, 909
 - pancreatic, 932
 - of Santorini, 932
 - of Wirsung, 932
- Ductless glands, 889
- Ducts, ejaculatory, 1126
- Ductus arteriosus, 262
 - choledochus, 941
 - endolymphaticus, 783
 - pneumaticus, 450
 - venosus, 261
- Dudgeon's sphygmograph, 382
- Duke and Howell's theory of cardiac inhibition, 319
- Duodenal juice, 931
- Dura mater, 716
- Dust, blood, 159
- Dynamic phase of respiratory cycle, 461
 - sense, 730, 785
 - theories of reproduction, 1117
 - theory of cortical function, 701
- Dynamograph, 81, 82
- Dyschromatopsia, 888
- Dysoxidizable substances, 510
- Dyspnea, 471, 525
 - heat, 475
- EAR; anvil bone of, 766
 - bones, 764, 766
 - movements, 767
 - external, 763
 - hair cells, 776, 777
 - hammer-bone, 765
 - inherent muscles of, 770
 - internal, 771
 - middle, 763, 764
 - sacculle, 771, 782
 - stirrup bone, 767
 - utricle, 771, 782
- Eardrum, 764, 765
- Ear-wax, 895
- Echinochrome, 160
- Eck fistula, 946
- Effectors, different types, 583
- Efferent nerve fibers of heart, 310
 - neuron, 109
- Ehrlich's side-chain theory of immunity, 249
- Einhoven's string galvanometer, 99, 286
- Ejaculation of semen, 1127
 - spinal center for, 596
- Ejaculatory ducts, 1126
- Elasticity of muscle, 65
- Electric conductivity of blood, 165
 - current, axial, in nerve, 136
 - constant ascending, reaction of nerve to, 142
 - descending, reaction of nerve to, 142
 - reaction of normal and abnormal nerve and muscle to, 142
- demarcation, 103
- external resistance, 58
- in muscles, phases, 106
- internal resistance, 58
- interrupted, reaction of normal and abnormal nerve and muscle to, 142
- making and breaking, 60
- measurement, 58
- of action, 103
 - in nerve, 137
 - wave of negativity and, relation of nerve impulse to, 138
- of injury, 103
 - alteration theory of, 104
 - in nerve, 135
 - molecular theory of, 104
- of rest, 103
- types, 62
- stimulation of muscle, 57
- stimuli, 35
- theory of light stimulation of retina, 840
 - of nerve conduction, 133
 - variations of heart, 286
- Electricity, animal, 99
- Electrocardiogram, 287
 - auricular complex, 288
 - ventricular complex, 288
- Electrocardiograph, 287
- Electrocardiography, 286
- Electrodes, non-polarizable, 59
- Electrolytes, 1025
- Electrometer, capillary, Lippmann's, 101
- Electromotive force, 58
- Electronegative oxygen, 510
- Electrotonic condition of nerve, method of testing, 146
 - differences on making and breaking galvanic current, 144
- Electrotonus, 142, 143
 - extrapolar, 143
 - intrapolar, 143
 - physical, 143
 - physiological, 143
- Embolus, 218
- Embryo, development 1135
 - nutrition of, 1142
- Emission of semen, spontaneous, 1128
 - theory of light, 794
- Emmetropia, 855
- Emphysema, 457
- Encephalon, 716
- Endocardium, 263
- Endocrine organs, 953
- Endo-enzyme, 988

- Endogenous protein, 1049
 Endolymph, 771
 Endoneurium, 111
 End-organs of nerve-fiber, 113
 End-products of protein metabolism, 1050
 Energy, chemical, 729
 different manifestations of, 727
 vibratory, 728
 Engelmann's artificial muscle, 49
 method of testing electrotonic condition of nerve, 145
 theory of muscle contraction, 49
 Enterograph, 1013
 Enterokinase, 932, 935, 950, 997
 Entoptic phenomena, 854
 Enzymes, 981
 muscle, 87
 of pancreatic juice, 935
 Eosinophilic leukocytes, 200
 Ependyma, 663
 Epicardium, 263
 Epidermis, 893, 1123
 Epiglottis, function, 543
 Epilepsy, Jacksonian, 677
 traumatic, 677
 Epimysium, 43
 Epinephrin, action on autonomic nervous system, 974
 action on circulation, 971
 Epineurium, 111, 970, 971
 Epiphysis cerebri, 980
 Equilibrium, nerve of, 651
 nitrogen-, 1049
 sense of, 781
 Erb's reaction, 156
 Erectile tissues, male, 1126
 Erection of penis, 1127
 spinal center for, 596
 Erepsin, 932, 935, 950, 997
 Ergograph, 81, 82
 Ergotoxin, effect of, on salivary secretion, 916
 Erythroblasts, 196
 Erythrocytes, 172. See also *Blood corpuscles, red*.
 Erythro-dextrin, 993
 Esophagus, function of, in deglutition, 1002
 Esthesiometer, 735
 Estrus, 1133
 Ether, 794
 luminiferous, 794
 Ethereal odors, 747
 Ethylene, 187
 Euglobulin, 172
 Euler and Huyghens' undulatory theory of light, 794
 Eustachian tube, 764, 769
 valve, 262
 Evolution, Darwin's theory of, 1121
 Excised heart, 331
 Excitation, fatigue of, 571
 of muscle, 51
 Excretion, 1064
 Exercise, muscular, effect of, on metabolism, 1054
 Exo-enzyme, 988
 Exogenous protein, 1049
 Expiration, 448, 461
 Expiratory movement, 470
 Expired air, character of, 486
 Explosive sounds, 554
 Extensibility of muscle, 65
 External ear, 763
 Exteroceptors, 730
 Extractives of muscle, 87
 Extramural circulatory system, 428
 Extrasystole, 338
 cause, 341
 Extravascular coagulation of blood, 211
 Extrinsic muscles of inspiration, 466
 Eye, 803
 anterior chamber, 806
 constant optical defects, 853
 effect of adrenalin on, 975
 electrical variations in, on vision, 844
 functions, 804
 human, accommodation of, 822
 limit, 828
 proofs, 823, 824
 range, 828
 humors of, 237
 optical defects of, acquired, 855
 inconstant, 855
 posterior chamber, 806
 protective appendages, 803
 reduced, 846
 refraction of, abnormalities in, 853
 refractive power of, ophthalmoscopic test, 863
 shadow test, 867
 schematic, 846
 sensory ligament, 821
 teeth, 1001
 visual axes of, secondary, 837
 axis of, 837
 white of, 805
 Eyeball, 803
 anterior cavity, 805
 general structure, 803, 804
 measurements, 804
 minute structure, 805
 movements of, 869, 870
 posterior cavity, 805
 sclera, 805
 Eyelids, 806
 closure of, center for, 641
 FACIAL muscles, reflexes from, 599
 nerve, 650
 Facilitation, 573
 Falsetto voice, 551
 Falx cerebri, 716
 cerebelli, 716
 Faradaic current, 62
 Far-point of vision, 828
 Far-sightedness, 860

- Fasciculus anterior proprius, 613
 anterolateralis superficialis, 613
 cerebrospinalis anterior, 612
 lateralis, 613
 cuneatus, 613
 gracilis, 613
 lateralis proprius, 613
 longitudinal, inferior, 661
 longitudinal, superior, 661
 occipitofrontal, 661
 spinocerebellaris, 613
 uncinate, 661
- Fatigue, auditory, 780
 effect of, on muscle contraction, 80
 muscle, chemistry of, 89
 Treppe phenomenon, 90
 nerve, 139, 140
 of depression, 571
 of excitation, 571
 of nerve cells, 568
 cause, 570
 of sense-organs, 732
 reflex, 585
 substances, 90
- Fat, body, source of, 1044
 carbohydrate-, 1041
- Fats, absorption of, 1030
 chemical theory, 1031
 mechanistic theory, 1031
 metabolism of, 1044
 of milk, 902
 reaction of intestinal bacteria on, 997
 utilization, 1046
- Fat-splitting enzyme of saliva, 994
- Fatty degeneration, 1047
- Faucial tonsils, crypts of, 906
 function, 906
 removal of, effects, 907
- Feces, character, 1035
 contents, 1035
 formation, 1035, 1036
- Fechner's psychophysical law, 733
- Fecundation, 1117
- Female reproductive organs, 1122
- Fenestra ovalis, 764
 rotunda, 764
- Fermentation, 987
 of milk, alcoholic, 901
- Ferments, 987
 classification, 988
 deamination of, 990
 decarboxylation of, 990
 hydrolysis by, 990
 intermediate products of, 991
 manner of action, 990
 nature of, 988
 number of molecules in action of, 991
 optimum temperature for, 991
 oxidation of, 991
 reduction of, 991
 respiratory, 513
 reversibility of, 991
 self-inhibition of, 962
- Fertilization, 1117
 of ovum, 1118
- Fetal life, circulatory system in, 260, 261
- Fetid odors, 747
- Fetus, oxygen requirement of, 1142
- Fever, high, 1106
 Liebermeister's neurogenic theory, 1107
 low, 1106
 toxogenic theory, 1107
- Fiber cells of Retzius, 786
- Fibers, fillet system of, 661
 frontopontine, 661
 moss, of cerebellum, 708
 muscle, 43, 44
 intermediate discs, 44
 transverse discs, 441
 temporopontine, 661
 tendrils, of cerebellum, 708
- Fibrillæ, 44
- Fibrillar hypothesis of nervous system, 565
 theory of structure of protoplasm, 24
- Fibrillation, auricular, 279
 of heart muscle, 279
 ventricular, 279
- Fibrin, 212, 217
- Fibrin-ferment, 171, 215
- Fibrinogen, 170, 171, 213, 216
 tissue-, 222
- Field, visual, 851
- Figures, Müller-Lyer, 878
 Purkinje's, 839
- Filiform papillæ of tongue, 748
- Fillet, median, 684
 system of fibers, 661
- Filtration theory of formation of lymph, 238
 of salivary secretion, facts disproving, 917
 of secretions, 892
 of urinary secretion, 1067
- Filum terminale, 604
- Fish, circulatory system of, 256
 swim-bladder of, 450
- Fistula, Eck, 946
- Flavors in diet, 1062
- Flechsig's column, 613
 tract, 617
- Fleischl's hemoglobinometer, 191
- Flesh, goose, 894
- Fluoroscopic examination of intestinal movements, 1013
- Focus, virtual, 798
- Follicles, Graafian, 1129
 hair, 893
 primordial, 1129
- Fontana, spaces of, 805
- Food, 986
 bolus, 1001
 effect of, on arterial blood pressure, 371
 nutritive value, 1058
- Foodstuffs, 986
 history of, in body, 1037

- Foodstuffs, reduced, absorption of, from alimentary canal, 1022
- Foramen ovale, 262
- Foramina Thebesii, 264, 428
- Forebrain, 663, 664
- Fovea centralis, 836
- Fragrant odors, 747
- Fränkel's theory of menstruation, 1134
- Frank's instrument for registering heart-sounds, 290
- membrane manometer, 297
- Fraunhofer lines of spectrum, 193
- Friction of blood, 166
- sounds, 554
- Frog, compound, 1116
- preparation, rheoscopic, 104, 105
- Frontal association area, 699
- Frontopontine fibers, 661
- Fundus of stomach, movements of, 1005
- Fungiform papillæ of tongue, 748
- Funiculus, anterior, 612
- lateral, 613
- posterior, 613
- Fusion of colors, 880
- Gad's pneumatograph, 480
- Galactosids of nerve, 114
- Gall's system of craniotomy, 672
- Gall-bladder, 939
- innervation, 942
- Galvanic current, 62. See also *Electric current, constant*.
- Galvanism, 99
- Galvanometer, 99
- string, Einthoven's, 286
- for measuring speed of nerve conduction, 130
- Galvanotony, 152
- Galvanotropic reaction, 789
- Ganglia, basal, 703
- roof, of cerebellum, 708
- Ganglion, Bidder's, 318, 332
- in peripheral nervous system, 111
- intervertebral, 619
- Remak's, 318, 332
- spirale, 777
- Garlic odors, 747
- Gärtner's method of estimating hemoglobin, 191
- Gases, absorption of, by blood, 497
- by liquids, 496
- diffusion, 446
- extraction of, from blood, 497
- interchange of, between blood and tissues, 496
- between tidal air and blood, 488
- chemical theory, 494
- physical theory, 489
- in placenta, 451
- Gaskell's trophic theory of cardiac inhibition, 319
- Gastric artery, 433
- cells, central or chief cell of, 920
- glands, 918
- Gastric glands, histological changes in secretion, 920
- of cardiac end, 919
- of fundus, 919
- oxyntic cells of, 920
- parietal cells, 920
- hunger, 754
- juice, 920
- acidity, 923
- antiseptic action, 994
- artificial, 922
- effect of appetizers on, 930
- function, 993
- hydrochloric acid of, 923
- inverting action of, 994
- methods of obtaining, 921
- origin of active principles, 920
- psychic element in formation, 930
- secretion, nervous control, 928
- regulation of, 926
- study of, by psychic feeding, 930
- by sham feeding, 930
- mucosa, internal secretion of, 967
- secretin, 927
- secretions, 918
- Gastrin, 927, 931
- Gastro-enterostomy, 1010
- Gemmules, lateral, 108
- Genital organs, female, 1122
- internal secretions of, 981
- male, 1122
- Geometrical center of spherical mirror, 796
- Germ cells, 1114
- dental, 1001
- special, 1001
- Germinal spot, 1130
- Giant cells, 207
- Gianuzzi, crescents of, 909
- Gills, 448
- structure, 449
- Glan and Vierordt's method of determining hemoglobin, 190
- Gland, pineal, 980
- pituitary, 977. See also *Pituitary gland*.
- prostate, 1126
- thymus, 951, 963. See also *Thymus gland*.
- thyroid, 951, 954. See also *Thyroid gland*.
- Glande interstitielle l'ovaire, 982
- Glands, acini of, 892
- adrenal, 967. See also *Adrenal glands*.
- Bartholin's, 1136
- Cowper's, 1126
- ductless, 889
- endocrine, 953
- gastric, 918. See also *Gastric glands*.
- intestinal, 948
- lacrimal, 807
- secretion, 807
- lobes and lobules, 892

- Glands, mammary, 897. See *Mammary glands*.
 meibomian, 809
 mucous, secretory product, 907
 parathyroid, 951, 954. See also *Parathyroid glands*.
 racemose, 892
 salivary, 908. See also *Salivary glands*.
 sebaceous, 894
 sexual, 982
 sweat-, 895
 tubular, 892
 tubulo-racemose, 892
 urethral, 1126
 Glans penis, 1126
 Globin, 183
 Globulin, cell-, 222
 Glossopharyngeal nerves, 534, 653
 function, 749
 Glottis, 540, 543
 Gluteal reflex, 598
 Glycocholic acid, 947
 Glycogen, 965, 1039
 disappearance of, in muscle, 89
 formation of, 1038
 Glycogenase, 513, 1039
 Glycogenesis, 1042
 Glycogenic center, 1042
 Glycogenolysis, 1039, 1042
 Glycolysis, 1042
 Glycosuria, adrenalin-, 975
 alimentary, 1043
 conditions causing, 966
 hepatic, 1043
 pancreatic, 1043
 phloridzin, 1043
 renal, 1043
 Goiter, colloid, 961
 springs, 958
 Golgi's cell, 607
 Golgi-Mazzoni corpuscles, 734
 Goll, column of, 613
 Goose flesh, 634, 894
 Gouty diathesis, 1051
 Gower's fluid, 177
 hemoglobinometer, 191
 tract, 613, 618
 Graafian follicles, 1129
 mature, 1130
 Grandry and Merkel, corpuscles of, 735
 Granula theory of structure of protoplasm, 24
 Granules, Nissl's, 108, 563, 564
 zymogen, 909
 Graphic method of recording arterial blood pressure, 368
 Graves' disease, 959
 Gray matter, cerebral, general arrangement, 657
 of spinal cord, functional basis, 606
 Green-blindness, 888
 Gréhant and Quinquaud's method of determining quantity of blood, 227
 Ground bundle, anterior, 613
 lateral, 613
 Growth, 29, 1109
 factor of, in metabolism, 1059
 movement by, 38
 Guanidin metabolism in thyroid gland, 963
 Guanine, 1051
 Guarana, 1063
 Gustometry, 751
 Guttural sounds, 554
 HAIR, 893
 cells of ampulla, activation of, 791
 of ear, 776, 777
 follicles, 893
 roots, 893
 Haldane and Smith's method of estimating oxygen tension in arterial blood, 492
 quantity of blood, 227
 Hammer-bone of ear, 765, 766
 Haptophore, 249
 Harmonies, 760
 Harmozones, 953
 Harvey's discovery of circulation of blood, 18
 Haustral churning, 1019
 Hayem's fluid, 177
 Head-pressure, 350
 Hearing, center, 689
 limits of, 780
 nerve of, 651
 sense of, 756
 Heart, 158, 255
 acceleration, 309
 character, 323
 accelerator nerve fibers, 311
 action current of, 286
 afferent nerve fibers of, 324
 beat, compensatory pause, 341
 effect of Ringer's solution on, 336
 internal stimulus, nature of, 336
 myogenic theory, 334
 neurogenic theory, 332
 origin, 331
 premature, 343
 refractory period, 338, 341
 center, 309
 compensatory hypertrophy, 343
 contraction, character, 274
 wave, path of, 275
 speed of, 275
 cycle of, 272
 number, 272
 phenomena in, 280
 time relation of, 305
 dilatation, 345
 effect of pressure on vagus on, 327
 efferent nerve fibers, 310
 electrical variations, 286
 excised, 331
 filling of, 292
 first sound, 290

- Heart, form of, changes, 281
 methods of registering, 281
 hypertrophy, 345
 impulse, 282
 inhibition, 309
 cause, 318
 character, 312
 escape of, 323
 Howell and Duke's theory, 319
 nature of, 315
 result, 320
 trophic theory of, 319
 inhibitor nerve fibers, 310
 measurements, 263
 mechanics of, 253
 muscle, fibrillation of, 279
 physiological properties, 338
 tissue, functional peculiarities, 331
 tonus of, 344
 musculature of, arrangement, 263
 nervous regulation, 309
 of amphibians, 256
 of birds, 258
 of reptiles, 257
 output, 302
 reflex death, 326
 second sound, 289, 291
 secondary augmentation, 314
 sounds, 289
 relationship between, 291
 third sound, 289, 292
 trigeminus reflex, 327
 valves, 263
 arrangement, 267 ,
 plan of, 306
 position of, in auricular systole, 307
 in ventricular systole, 307
 variations in arterial blood pressure,
 377
- Heart-block, 278
- Heat, dissipation of, 1089, 1097
 dyspnea, 475
 in animals, 1133
 of body, 1093. See also *Body temperature*.
 polypnea, 1095
 production, 1089, 1092, 1097
 basal, 1104
 ordinary, 1105
 sources, 1092
 spots of skin, 742
 total quantity, 1103
 unit of measurement, 1090
- Heat-accelerator centers, 1102
- Heat-inhibitory centers, 1102
- Heat-rays, 880
- Heidenhain's chemical or vitalistic
 theory of secretion, 892
 classification of salivary glands, 908
 theory of formation of lymph, 238
 of urinary secretion, 1068
- Held's bundle, 616
- Helicotrema, 773
- Helmholtz's detention theory of accom-
 modation of eye, 822
- Helmholtz's method of determining
 speed of nerve conduction, 129
 ophthalmometer, 858
 ophthalmoscope, 863
 phacoscope, 826
 resonator, 762
 resonance theory of hearing, 777
- Helweg's bundle, 616
- Hematin, 183, 188
 acid, spectrum of, 195
- Hematoblasts, 208
- Hematocrit, 159
- Hematoidin, 189
- Hematopoiesis, 197
- Hematopoietic function of faucial ton-
 sils, 906
 of spleen, 905
 tissues, 196
- Hematoporphyrin, 189, 1080
 spectrum of, 195
- Hemerythrin, 160
- Hemianopia, bilateral, 685
- Hemianopsia, 685, 696
- Hemic murmurs, 780
- Hemin, 188
 crystals, 188
- Hemiplegia, 679, 695
- Hemochromogen, 183, 188
 spectrum of, 195
- Hemoconia, 159
- Hemocyanin, 160
- Hemocytometer, Thoma-Zeiss, 176
- Hemodromograph, Chauveau and Lor-
 tet's, 405
- Hemodromometer, Volkmann's, 404
- Hemodynamics, 347
- Hemoglobin, affinity of, for carbon
 monoxid, 187
 and oxygen, compounds of, proper-
 ties, 185
 and stroma of red corpuscles, separa-
 tion, 181
 carbon monoxid, spectrum of, 194
 compounds, 186
 constituents, 183
 crystals, 184
 derivative compounds, 187
 spectroscopic analysis, 192
 determination, chronometric method,
 190
 clinical methods, 189
 estimation, Tallquist's method, 191
 nitric oxid, spectrum of, 194
 reduced, 183
 spectrum of, 193
 spectroscopic analysis, 192
- Hemoglobinometer, Fleischl's, 191
 Gower's, 191
 Hoppe-Seyler's, 191
- Hemolysins, 181
- Hemolysis, 181, 248
- Hemometer, 191
- Hemophilia, 221
- Hemophotographic method of estimat-
 ing hemoglobin, 191

- Hemopyrrol, 189
 Hemorrhage, 230
 Hemotachometer, Chauveau and Lortet's, 405
 Henderson's cardiometer, 304
 Henle's sphincter, 1128
 U-shaped loop, 1065
 Hepatic artery, 433
 glycosuria, 966, 1043
 plexus, 939
 Herbst, corpuscles of, 735
 Hering's method of estimating circulation time, 409
 theory of color vision, 886
 Hermann's core-conductor, 133
 demarcation current, 103
 Herpes zoster, 622
 Heteronymous diplopia, 872
 Heterophoria, 873
 Hibernating animals, respiratory quotients in, 515
 Hiccough, 482
 High fever, 1106
 Hill's micro-calorimeter, 1092
 Hindbrain, 663, 664
 Hippocampal commissure, 662
 Hippuric acid in urine, 1087
 Hirudin, effect of, on coagulation of blood, 225
 His's bundle, 264
 theory of neuroblasts, 559
 Holmgren's tests for color-blindness, 888
 Homoiothermal animals, 1093
 Homolateral effects of hemisection of spinal cord, 626
 Homonymous diplopia, 872
 Hoppe-Seyler's hemoglobinometer, 191
 indirect method of determining amount of blood corpuscles, 160
 theory of activation of oxygen, 512
 Hoppe-Seyler and Welker's chronometric method of determining hemoglobin, 190
 Hormones, 926, 952, 953
 Horopter, 874
 Horse blood, composition, 168
 talking, 692
 Howell and Duke's theory of cardiac inhibition, 319
 Humor, aqueous, 809
 vitreous, 810
 Humors of eye, 237
 Hürthle's angiometer, 383
 apparatus for estimating volume of blood stream, 395
 membrane manometer, 296
 Hunger, 753
 gastric, 754
 sense, 743
 somatic, 754
 Hutchinson's spirometer, 479
 Wintrich's modification, 479
 Huyghens and Euler's undulatory theory of light, 794
 Hyaloplasm, 24
 Hydraulic pressure, 347
 Hydremic plethora, 1074
 Hydrobilirubin, 948
 Hydrochloric acid, 952
 of gastric juice, 923
 Hydrodynamic pressure, 347
 Hydrolysis of ferments, 990
 Hydrolytic oxidations, 511
 Hydrostatic pressure, 347
 Hydrothorax, 457
 Hyperchlorhydria, 923
 Hypermetropia, 855, 860
 Hypermetry in cerebellar disease, 713
 Hyperosmotic solution, 1025
 Hyperpnea, 524
 Hyperpyrexia, 1106
 Hyperthermy, 1106
 Hyperthymusism, 964
 Hyperthyroidism, 957, 959
 Hypertonic solution, 1025
 Hypertrophy of heart, 345
 Hypnotic sleep, 724
 Hypogastric arteries, 262
 Hypoglossal nerve, 656
 Hypoleukocytosis, 201
 Hypophysin, 978
 Hypophysis cerebri, 977. See also *Pituitary gland.*
 Hyposmotic solution, 1025
 Hypothermy, 1106
 Hypotonic solution, 1025
 Hypoxanthine, 1051

 ICTERUS, 944
 Ileocecal valve, 1017
 Illusions, optical, 876
 touch, 739
 Image, real, 797
 retinal, formation, 846, 848
 virtual, 798
 Images, Purkinje's, 839
 Immune body, 251
 Immunity, 245
 acquired, 246
 active, 246
 antibodies in, 247
 causes, 247
 complete, 245
 Ehrlich's side-chain theory, 249
 general, 246
 local, 246
 natural, 246
 nature of reactions in, 248
 partial, 245
 passive, 246
 permanent, 246
 phagocytosis in, 247
 temporary, 246
 Implantation of ovum, 1137
 Impulsus cordis, 282
 Inanimate material, 19
 Incus, 766
 Index of refraction, 798
 opsonic, 206
 Indican in urine, 1082

- Indirect blood transfusion, 231
 vision, 837
 Indol in urine, 1082
 Induced current, 62
 Induction coil, 62
 Inductorium, DuBois-Reymond, 63
 Infantilis, 957
 Infundibula, 452
 Infundibulum of pituitary gland, 977
 Infusion of blood, 230
 Inhibition, heart, 309
 of nerve cell, 574
 of reflexes, 588
 theory of sleep, 723
 Inhibitor nerve fibers of heart, 310
 Innervation of adrenal glands, 973
 of ciliary muscle, 830
 of gall-bladder, 942
 of iris, 817
 of larynx, 535, 547
 of mammary glands, 899
 of salivary glands, 911
 of stomach musculature, 1012
 of sweat-glands, 897
 Inorganic salts in diet, 1061
 Inotropic cardiomotor impulses, 315
 Insects, respiration in, 448
 Inspiration, 448, 461
 muscles of, 466
 Inspiratory movement, 466
 Inspired air, character of, 486
 Insufflation, constant, 486
 Intensity of sounds, 758
 Intercoastal muscles, action of, in respiration, 468
 Intermediary substance of nerve, 116
 Internal ear, 771
 secretions, 951
 classification, 952
 of gastric mucosa, 967
 of genital organs, 981
 of intestinal mucosa, 967
 Interoceptors, general, 730, 752
 special, 730, 743
 Interpolated systole, 343
 Interrupter, Neff's, 64
 Intervertebral ganglion, 619
 Intestinal bacteria, reaction of, on
 carbohydrates, 997
 on fats, 997
 on proteins, 998
 canal, absorption from, 1027
 glands, 948
 juice, 938
 function, 997
 secretion of, 949
 mucosa, internal secretion of, 967
 Intestine, large, divisions of, 1010
 movements of, 1017
 small, movements, 1013
 pendular motion, 1014
 Intestines, movements, 1013
 fluoroscopic examination, 1013
 nervous control, 1015
 vasomotor nerves of, 437
 Intra-abdominal pressure, changes in, 478
 Intra-auricular pressure, 297
 filling of auricles in, 299
 Intracardiac pressure, changes in, 292
 diastolic, 296
 mean, 296
 methods of registration, 292
 systolic pressure, 296
 Intracranial pressure, 441
 Intramural circulatory system, 428
 Intraocular pressure, 805, 810
 Intrapleural pressure, 457
 Intrapulmonic pressure, 457
 changes in, 478
 Intrathoracic pressure, 457
 cause of negativity of, 460
 changes in, 477
 Intravascular clotting of blood, 217
 lymph, 233
 Intraventricular pressure, 300
 Intrinsic muscles of inspiration, 466
 Inversion of retinal image, 848
 Invertase, 950
 Invertin, 931
 Inverting enzymes, 989
 Iodothylin, 952, 960
 Ionization theory of activation of oxygen, 511
 Iris, 811
 function, 812
 innervation of, 817
 Irritability of muscle, independent, 52
 of nerve, 124
 conductivity and, differentiation, 124
 of protoplasm, 35
 Ischiocavernosus muscle, 1127
 Islands of Langerhans, 932, 965
 Isometric myograms, 56
 Isosmotic solution, 1025
 Isotonic myograms, 56
 solution, 1025
 JACKSONIAN epilepsy, 677
 Jacobson's nerve, 912
 Janeway's sphygmomanometer, 369
 Jaw jerk, 599
 Jejunum, 1036
 Jensen's theory of muscle contraction, 50
 Johansson and Tigerstedt's cardiometer, 304
 KARYOKINESIS, 1111
 Kephalin, 222
 of nerve, 114
 Kephir, 901
 Ketosis, 1043
 Kidney oncometer, 398
 structure, 1064
 vasomotors of, 435
 Kinase, 170, 990
 Knee-jerk, 599
 König's resonator, 762

- Koumiss, 901
 Krause's corpuscle, 735, 736
 Kries' apparatus for recording capillary pressure, 376
 Krogh's microtonometer, 491
 Kühne's method of proving double nerve conduction, 127
 Kupfer's stellate cells, 207, 939
- LABIAL** sounds, 554
Labor, 1444
 abdominal press in, 1145
 average duration, 1145
 effect of, on arterial blood pressure, 371
 pains, 1144
 stages, 1145
Labyrinth, 763
 of ear, 771
 osseous, 771
Labyrinthine reflexes, 789
 tonus, 789
Lacrimal glands, 807
 secretion, 807
 lake, 808
Lactalbumin, 902
Lactase, 990, 997
Lactation, mammary glands during, 899
Lacteals, 235
Lactic acid of muscle, 87
 formation, 88
Lactoglobulin, 902
Lactose, 902
Ladd-Franklin theory of color vision, 887
Laennec's stethoscope, 757
Lake, lacrimal, 808
Laked blood, 181
Lamella, anterior homogeneous, of cornea, 805
 posterior homogeneous, of cornea, 805
Lamina basilaris, 775
 dental, 1001
 spiral, 772
Langenbeck's proof of accommodation of eye, 824
Langerhans, islands of, 932, 965
Laryngeal branch of vagus, superior, 534
 branches of vagus, inferior, 535
 chamber, 540
Larynx, 540
 artificial, 551
 cartilages of, 541
 examination of, in reflected light, 550
 general structure, 541
 innervation of, 535, 547
 ligaments of, 541
Laughing, 482
Law, Bell-Magendie, 620
 of degeneration, Wallerian, 621
 Weber's, 733
Lecithin, 948
 in blood, 169
 of nerve, 114
Lecithoprotein, 217
Léclanche cell, 57
Leech extract, effect of, on coagulation of blood, 225
Lens, biconcave, 800
 refraction by, 803
 biconvex. See *Biconvex lens*.
 crystalline, 820
 changes in shape and refractive power, 827
 wabbling of, 826
Lenses, achromatic, of Dollard, 816
 refraction by, 799
 varieties, 799
Leukocytes, 200
 basophilic, 200
 diapedesis, 206
 eosinophilic, 200
 mononuclear, 200
 polymorphonuclear, 200
 polynuclear, 200
 transitional type, 200
Leukocytosis, 201
 assimilation, 201
 pathological, 201
Leukocythemia, 904
Leukopenia, 201
Levers, different systems, 47, 48
Leydig, cells of, interstitial, function, 984
Lieberkühn, crypts of, 908, 949
Life, general conditions, 33
 phenomena, 29
 spontaneity of, 33
 structural basis of, 21
Ligaments of larynx, 541
Light, cause of, 794
 corpuscular theory, 794
 emission theory, 794
 nature of, 794
 qualities of, 879
 reflection of, 795
 reflex, 648, 812
 sources of, 794
 stimulation by, chemical and physical
 changes in retina from, 840
 undulatory theory, 794
 velocity of, 794
 white, 879
Lindemann's method of determining quantity of blood, 228
Linea diaphragmatica, 464
Lines, Zöllner's, 878, 879
Lingual tonsils, 907
Linguopalatal sounds, 554
Lipase, 513, 935
 of saliva, 994
Lipins of muscle, 86
Lipochrome, 171
Lipoids, 25
 of nerve, 114
Lipolytic action of pancreatic juice, 996
 enzymes, 989
Lippmann's capillary electrometer, 101

- Liquid, flow of, through elastic tubes, 351
 through rigid tubes, 349
- Liquor amnii, 1140
 folliculi, 1129
 spinalis, 605
- Lissauer's bundle, 616
- Liver, 938, 951, 964
 blood supply, 938
 disintegration of red corpuscles by, 198
 extirpation, 945
 function, 940
 internal secretory power, 964
 origin of urea in, 1084
 vasomotor nerves of, 438
- Living substance, 17
 metabolic function, 20
 reproduction of, 32
- Lobes of glands, 892
- Lobules of glands, 892
- Lobuli complicati of cerebellum, 706
- Lobulus medianus posterior of cerebellum, 706
 simplex of cerebellum, 706
- Lobus quadratus anterior of cerebellum, 706
- Localization, cerebellar, 713
 cerebral, 671, 681
 tactile, 736
- Locomotion, action of striated muscle in, 46
 lever movements in, 47
- Loring's ophthalmoscope, 864
- Low fever, 1106
- Lower extremity, motor points in, 153
- Ludwig's filtration theory of urinary secretion, 1067
 mechanistic theory of secretion, 892
- stromuhr, 395
 theory of formation of lymph, 237
- Lumbar puncture, 720
- Luminiferous ether, 794
- Luminosity, 880
- Lung, air-cells or alveoli of, 451
 amphibian, 451
 birds', 451
 capacity, estimation of, 481
 changes in position, in respiration, 475
 collapse, 457
 complex, 451
 elementary, 447, 448
 structure and function, 445
 general topography, 454
 mammalian, 452
- Lungmotor, 484
- Lutein, 171
- Luxus consumption, 1057
- Lymph, 158, 233
 as protective mechanism, 245
 augmentation of flow, 240
 constituents, 235
 factors controlling flow, 243
 formation, 233, 237
- Lymph, intravascular, 233
 properties, 233, 234
 sources, 237
- Lymphagogues, 240
- Lymphatic secretions, 903
- Lymphatics, distribution of, 234
- Lymphocytes, types, 200
- Lymph-hearts of amphibia and birds, 244
- MACROCYTES, 175
- Macrophages, 198
- Macrosmatic animals, 690
- Macula acustica, 783
 sacculi, function, 783
 utriculi, function, 783
- Magnesium sulphate, effect on speed of nerve conduction, 133
- Malapterurus, electrical organ of, double nerve conduction in, 123
- Male erectile tissues, 1126
 reproductive organs, 1122
- Malleus, 765, 766
- Malpighian corpuscles, 904
- Maltase, 950, 990, 997
- Mammalian lung, 452
- Mammals, alimentary canal of, 998
 circulatory system in, 258
 spinal reflexes in, 595
- Mammary glands, 897
 during lactation, 899
 effect of pituitrin on, 979
 histological character, 898
 in pregnancy, 898, 1138
 innervation of, 899
 relation to female sexual organs, 899
- Mammillary reflex, 598
- Man, normal diet of, 1058
- Manometer, membrane, 296
 mercury, 293,
- Marey's pneumograph, 473
 sphygmograph, 382
 tambour, 285
- Mast-cells, 200
- Mastication, 998, 1000
 center for, 641
- Mastoid antrum, 764
 cells, 764
- Mate, 1063
- Material, animate, 19
 inanimate, 19
- Matteucci's current of rest, 103
- Mayer curves, 393
 theory of muscle contraction, 49
- Maximal stimuli, 34
- Maxwell's color wheel, 880
- McDougall's theory of muscle contraction, 50
- Meatus, auditory, 763
 external, 764
- Mechanical block theory of sleep, 723
 imprint theory of light stimulation of retina, 840
 stimuli, 33

- Mechanical theory of urinary secretion, facts contradicting, 1068
 Mechanistic theory of fat absorption, 1031
 of secretions, 892
 Media, transparent, 795
 Mediastinum, 455
 Medulla oblongata, 640
 as automatic center, 641
 as reflex center, 640
 function, 640
 Medullary sheath of nerve, 111
 substance of nerve-fiber, 113
 Megakaryocytes, 210
 Megalocytes, 175
 Meibomian glands, 809
 Meigg's theory of muscle contraction, 50
 Meissner, corpuscles of, 734
 Membrana granulosa, 1130
 vestibularis, 775
 Membrane, basal, 775
 basilar, 772
 manometer, 296
 nictitating, 807
 of Reissner, 775
 tectorial, 777
 tympanic, 765
 Membranous canal of cochlea, 775
 Mendel's law, 1120
 Mendenhall and Cannon's coagulometer, 220
 Ménière's disease, 790
 Menopause, 1132
 Menstrual blood, coagulability of, 226
 Menstruation, 1132
 effect of, on arterial blood pressure, 371
 ovulation and, relation, 1133
 symptoms during, 1132
 theories of cause, 1133
 Mercury manometer, 293
 Mesencephalon, 664
 Mesenteric artery, inferior, 433
 superior, 433
 Mesoporphyrin, 189
 Metabolic function of living matter, 20
 requirements of body, 1052
 Metabolism, 29, 30, 985
 effect of adrenalin on, 975
 of age and sex on, 1054
 of muscular exercise on, 1054
 of sleep on, 1054
 of temperature on, 1054
 excessive, 1057
 factor of growth in, 1059
 normal, 1055
 of carbohydrates, 1038
 of fats, 1044
 of proteins, 1048
 end products of, 1050
 specific dynamic action of proteins in, 1059
 Metaphase of mitosis of cell, 1111
 Metchnikoff's phagocytosis, 39
 Metestrus, 1133
 Methemoglobin, 186
 spectrum of, 194
 Methylpropylpyrrol, 189
 Micro-calorimeter of Hill, 1092
 Microcytes, 175
 Microscope, examination of circulation by, 408
 Microsmatic animals, 690
 Microtonometer, Krogh's, 491
 Micturition, abdominal press in, 1077
 mechanism of, 1077
 reflex center for, 596, 1077
 spinal center for, 596
 Midbrain, 663, 664
 reflex inhibition by, 589
 Middle ear, 763, 764
 Migration of ovum, 1135
 of spermatozoa, 1136
 Milk, alcoholic fermentation, 901
 amount required by infant, 901
 secreted by mother, 901
 carbohydrate, 902
 coagulation, 901
 composition, 901
 cow's, humanized, 903
 human and cows' comparison, 902, 903
 properties, 900
 protein, 902
 salts of, 902
 skin formation from boiling, 901
 teeth, 1001
 Milk-curdling action of pancreatic juice, 996
 of saliva, 994
 Milk-sugar, 902
 Mind-blindness, 688
 Mind-deafness, 688
 Minimal air, 481
 stimuli, 34
 Miosis, 817
 Mirror, plane, reflection from, 796
 spherical, 796. See also *Spherical mirror*.
 Mitosis, 1111
 Mitral valve, 268
 Moderator bands, 267
 Modiolus, 772
 Molecular motion, Brownian, 37
 theory of current of injury, 104
 Monakow's bundle, 616
 diaschisis effect of, 701
 Mononuclear leukocytes, 200
 Monosaccharides, 987
 Monticulus of cerebellum, 706
 Morgagni, ventricles of, 545
 Morse's key for making and breaking electrical current, 61
 Morula, 1119
 Moss fibers of cerebellum, 708
 Mosso's ergograph, 81, 82
 plethysmograph for arm, 399
 Motion, 36. See also *Movement*.

- Motor aphasia, 694
 area a true center, 676
 ablation of, effects, 679
 of cerebrum, 671
 location, 673
- Motor end-organ or effector, location of, 415
 neuron, 109
 paralysis from hemisection of spinal cord, 626
 points in lower extremity, 153
 in upper extremity, 152
- Motor-plate of muscle, 51
- Mountain sickness, 519
- Mouth-to-mouth method of artificial respiration, 484
- Movement, 36
 ameoid, 38
 by changes in cell turgor, 37
 in specific gravity, 38
 by growth, 38
 by secretion, 38
 by swelling of cell-walls, 37
 ciliary, 39
 molecular, Brownian, 37
 muscular, 42
 period of contraction, 43
 of relaxation, 43
 passive, 36
 sense of, 785
 types, 36
- Mucin, 907
 action of, 993
- Mucous glands, secretory product, 907
 secretions, 903
- Mucus, 907
- Müller's theory of muscle contraction, 50
- Müller-Lyer figures, 878
- Murmur, bronchial, 477
 hemic, 780
- Musæ volitantes, 854
- Muscarin, effect on inhibitor reaction of heart, 316, 317
- Muscle, abnormal, reaction to constant and interrupted electrical currents, 142
 absolute power of, 95
 artificial, of Engelmann, 49
 as electrogenic organ, 98
 as thermogenic organ, 97
 bulbocavernosus, 1127
 carbohydrates, 86
 cardiac, 42
 chemistry of, 85
 ciliary, innervation of, 830
 coagulation-rigor, 93
 contracting, chemical changes in, 87
 contraction, 48
 character of, 70
 factors varying, 76
 effect of drugs and chemicals on, 79
 of duration of stimulus on, 77
 of fatigue on, 80
- Muscle, contraction, effect of load on, 77
 of muscle substance on, 77
 of strength of stimulus on, 76
 of veratrin on, 79
 Engelmann's theory, 49
 fusion, 71
 graphic registration, 53
 induced, 104
 influence of temperature on, 78
 Jenson's theory, 50
 McDougall's theory, 50
 maximal, 77
 Mayer's theory, 49
 Meigs' theory, 50
 minimal, 77
 Müller's theory, 50
 Ranvier's theory, 50
 refractory period, 72
 registration, muscle-nerve preparation for, 53
 methods, 54
 Schäfer's theory, 50
 summation, 71
 supramaximal, 77
 tetanic, 72
 thermodynamic theory, 49
 threshold, 76
 Verworn's theory, 50
 voluntary, 73
 wave, 68
 Weber's theory, 49
- contracture, 74
 clonic, 75
 tonic, 75
- Crampton's, 822
- cremaster, 1123
- crico-arytenoid, lateral, 547
 posterior, 547
- different phases of electric currents in, 106
- direct stimulation, 52
- disappearance of glycogen in, 89
- effect of sodium chlorid on, 80
- elasticity, 65
- electric currents in, phases, 106
 stimulation, 57
 variations in, character, 103
 compensation method of detecting, 102
- energy, production of, 93
- enzymes, 87
- excitation, 51
- extensibility, 65
- extractives, 87
- fatigue, Treppe phenomenon, 90
- fiber, 43, 44
 intermediate discs, 44
 transverse discs, 44
- fibrillæ, 44
- forms of energy liberated by, 93
- general composition, 85
- heat rigor, 79
 thermoelectric method of measuring, 97

- Muscle human, degenerated, law of
 contraction, 155
 indirect stimulation, 52
 inorganic constituents, 86
 irritability of, independent, 52
 ischiocavernosus, 1127
 lactic acid in, 87
 formation, 88
 lipins, 86
 methods of stimulation, 53
 motor plate, 51
 negative variation of primary demar-
 cation current in, 107
 non-striated, 42
 normal human, law of contraction,
 150
 reaction to constant and inter-
 rupted electrical currents, 142
 orbicularis palpebrarum, 807
 pale, 44
 physiology of, 17
 pigments, 87
 production of carbon dioxid by, 88
 proteins, 85
 purins, 87
 red, 44
 retractor bulbi, 870
 lentis, 821
 simple twitch, 70
 smooth, character of contraction, 83,
 84
 tonicity of, 83
 sound, 69
 spindles, function, 784
 stapedius, 765
 stimulation, unipolar method, 151
 effects of, 154
 striated, 42
 action in locomotion, 46
 stroma, 85
 proteins of, 86
 subminimal stimuli, summation,
 76
 substance, effect of, on contraction,
 77
 summation of contractions, 340
 of stimuli, 340
 tensor tympani, 765
 thyro-arytenoid, 547
 tissue, cardiac, 46
 effect of adrenalin on, 975
 peculiarities, 65
 smooth, 45
 structure, 43
 tonicity of, 66
 trophic, state, 67
 water-rigor, 93
 work performed by, 94
 Muscle-curve, latent period, 71
 period of contraction, 70
 of relaxation, 70
 Muscle-nerve preparation for register-
 ing muscle contraction, 53
 Muscle-plasma, proteins of, 86
 Muscle-spindle, 51
- Muscles, of ear, inherent, 770
 of inspiration, 466
 accessory, 466
 extrinsic, 466
 intrinsic, 466
 normal, 466
 papillary, 267
 Muscular exercise, effect of, on arterial
 blood pressures, 371
 respiratory quotient in, 515
 movement, 42
 period of contraction, 43
 of relaxation, 43
 Musculature, skeletal, 42
 visceral, 42
 Musculi pectinati, 264
 Musical sounds, 758
 Mydriasis, 817
 Myelin sheath of nerve, 111
 function, 116
 Myeloplaxes of bone-marrow, 207
 Myocardium, 263
 Myogen, 86
 Myogenfibrin, 86
 Myogenic theory of heart beat, 334
 of peristalsis, 1016
 Myograms, isometric, 56
 isotonic, 56
 Myography, 54
 Myoids, 42
 Myopia, 855, 859
 Myosin, 86
 Myosinfibrin, 86
 Myxedema, 957, 958
- NARCOSIS, 716, 725
 Narcotics, effect of, on speed of nerve
 conduction, 133
 Nasal sounds, 554
 Nauseating odors, 747
 Near-point of vision, 828
 Near-sightedness, 859
 Neff's interrupter, 64
 Negative variation of primary demar-
 cation current in muscle, 107
 Neopallium, 665
 Nerve, abducens, 650
 abnormal, reaction to constant and
 interrupted electrical currents, 142
 accessory, 655
 auditory, 651
 axial current in, 136
 axis-cylinder, function, 116
 band fiber, 121
 cells, fatigue of, 568
 cause, 570
 inhibition of, 574
 refractory period, 571
 summation of stimuli in, 572
 center, 111
 chemistry, 114
 cholesterin, 114
 compression-paralysis, 131
 conduction, centrifugal, 126
 centripetal, 126

- Nerve, conduction, chemical theory, 134
 direction, 125
 double, in electrical organ of *Macropodus*, 128
 Kühne's method of proving, 127
 law of, 126
 electrical theory of, 133
 forward, law of, 126
 nature of, 133
 speed, 128
 effect of alcohol on, 133
 of anesthetics on, 133
 of carbon dioxide on, 133
 of immersion in water on, 132
 of magnesium sulphate on, 133
 of narcotics on, 133
 of temperature on, 132
 factors altering, 131
 Helmholtz's method of determining, 129
 string galvanometer for measuring, 130
 wave of negativity in, 134
 theory of, 133
 conductivity, 124
 current of action in, 137
 of injury in, 135
 degeneration, 117
 ascending, 120
 descending, 120
 morphological changes, 120
 primary, 118
 retrogressive, 119, 122
 secondary, 118, 621
 tertiary, 119
 Wallerian law of, 119
 depressor, 325, 329
 dorsalis penis, 1129
 electrotonic condition, method of testing, 146
 energies, specific, doctrine of, 730
 erigens, 1129
 facial, 650
 fatigue, 139, 140
 function, 115
 of different parts, 116
 galactosids, 114
 glossopharyngeus, 534, 653
 function, 749
 going to sleep, 131
 human, degenerated law of contraction, 155
 hypoglossal, 656
 ileo-inguinalis, 1129
 impulse, relation to wave of negativity and action current, 138
 inorganic salts in, 115
 intermediary substance, 116
 irreciprocal conduction, 115
 irritability, 124
 conductivity and, differentiation, 124
 kephalin, 114
 lecithin, 114
- Nerve, liberation of energy by, 134
 lipoids, 114
 medullary sheath, 111
 metabolism during activity, 138
 methods of stimulation, 53
 myelin sheath, 111
 function, 116
 neurilemma, function, 117
 normal human, law of contraction, 150
 reaction to constant and interrupted electrical currents, 142
 oculomotor, 647
 of equilibrium, 651
 of hearing, 651
 of Jacobson, 912
 olfactory, 644
 optic, 645
 phenomena of conduction, 124
 physiology, 17, 108
 plexus, 112
 pneumogastric, 654. See also *Vagus nerve*.
 potassium in, 115
 primitive sheath, 111
 proteins, 114
 pudendus, 1129
 reaction of, to ascending constant electric current, 142
 to descending constant electric current, 142
 to polarization current, 142
 receptor substance, 116
 refractory period, lengthening of, 141
 regeneration, 122
 embryonic fibers in, 123
 morphologic changes, 122
 stimulation, unipolar method, 151
 effects, 154
 structure, 111
 tetanus of, secondary, 148
 tissue, assimilative changes, 139
 dissimilative changes, 139
 refractory period, 139
 trigeminus, 534, 649
 trochlear, 649
 vagus, 654. See *Vagus nerve*.
 Nerve-fiber, 111
 axis cylinder, 113
 band, 121
 degenerating, histology, 123
 end-organs, 113
 medullary substance, 113
 neurilemma, 113
 retrogressive degeneration, 611
 thickness, 112
 Nerve-fibrils, 112
 Nerves, cranial, 642
 functional system of, 642
 glossopharyngeal, 534
 in lower extremity, 153
 Nervous depressants, effect on body temperature, 1106
 regulation of respiration, 528
 system, anatomic division, 557

- Nervous system, autonomic, 627
 action of epinephrin on, 974
 afferent conduction in, 635
 cerebrospinal system and, connections between, 631
 characteristics, 629
 function, 630
 central, 557
 mass, 557
 cerebrospinal, autonomic system and, connections between, 631
 cervical sympathetics, 631
 chemical grounds, 557
 cranial, 631
 fibrillar hypothesis, 565
 functional arrangement, 565
 grounds, 557
 significance, 557
 unit, 574
 histological grounds, 557
 joining of reflex circuits, 580
 lessening irritability of, reflex inhibition from, 590
 neuron concept of, 558
 parasympathetic, 627, 631
 peripheral complex, 557
 protective mechanisms, 706, 716
 reflex circuit, 575
 concept, 574
 evolution into reaction system, 578
 rudimentary, a reflex system, 376
 sacral sympathetic, 631
 structural arrangement, 557
 unit, 558
 subdivisions, 557
 sympathetic, 627
 thoracic sympathetic, 631
 visceral, 621
 Waldeyer's neuron doctrine of, 565
 arguments in favor, 567
- Nervus accelerans, 310
 perinei, 1129
- Neurilemma, 111
 of nerve, function, 117
 of nerve-fiber, 113
- Neurit, 108
- Neuroblast, 108, 559
- Neurogenic theory of fever, 1107
 of heart beat, 332
 of peristalsis, 1016
- Neuroglia, 108
- Neurokeratin, 113
- Neuron, 108, 558
 afferent, 109
 concept of nervous system, 558
 conducting paths, 108
 doctrine of nervous system, Waldeyer's, 565
 arguments in favor, 567
 efferent, 109
 external characteristics, 558
 form and size, 108
 function, 109
 internal characteristics, 563
- Neuron, motor, 109
 sensory, 109
 types of, 560, 561, 562
- Neutral salts, effect of, on coagulation of blood, 223
- Neutrophile granules, 200
- Neutrophiles, 199
- New-born infant, respiration in, 460
- Newton's emission or corpuscular theory of light, 794
- Nicotin, effect on inhibitor reaction of heart, 316
 on salivary secretion, 916
- Nictitating membrane, 807
- Nissl's granules, 108, 563, 564
- Nitric oxid hemoglobin, spectrum of, 194
- Nitrogen, amino-, 1051
 elimination of, in starvation, 1053
 excretion of, premortal rise, in starvation, 1053
 function, 447
 in blood, condition of, 507
 relation to sulphur, in starvation, 1053
- Nitrogen-equilibrium, 1049
- Nobili's galvanometer, 99
- Node, sino-auricular, 277
- Nodes of Ranvier, 113
- Noises, 757
 perception of, 780
- Non-polarizable electrodes, 59
- Non-striated muscle, 42
- Non-threshold substances, 1073
- Normoblasts, 197
- Novain, 87
- Nuclein, 26, 29
- Nucleoproteids, 26
 tissue, 222
- Nucleoprotein, 171
- Nucleus in central nervous system, 111
 of cell, 24
 cytoplasm and functional relation, 27
 cleavage, 1119
 segmentation, 1119
- OBESITY, 1047
 Banting's cure, 1056
- Occipitofrontal fasciculus, 661
- Oculomotor nerve, 647
- Odors, classification, 747
- Odores factores, 747
 intermediæ, 747
 suaveolentes, 747
- Ohm, 58
- Old-sightedness, 830
- Olein of milk, 902
- Olfactometer of Zwaardemaker, 746
- Olfactometry, 745
- Olfactory bulb, 644
 cells, power of reaction, 745
 specific action, 744
 center, 644, 690
 nerve, 644

- Olfactory nucleus, secondary, 644
 organ, structure, 743
 sensations, qualitative differences in, 747
 tract, 644
 Oligocythemia, 180
 Olivospinal tract, 616
 Oncometer, kidney, 398
 splenic, 398
 Oocyte, 1129
 Opaque bodies, 795
 Ophthalmodiaphanoscopy, 864
 Ophthalmometer, Helmholtz's, 858
 Ophthalmoscope for testing refractive power of eye, 863
 Helmholtz's, 863
 Loring's, 864
 Ophthalmoscopy, direct, 864
 indirect, 867
 Opsonic index, 206
 Opsonins, 205
 Optic defects of eye, acquired, 855
 inconstant, 855
 disc, 834
 illusions, 876
 nerve, 645
 thalamus, 703
 Optics, 794
 physiological, 794
 Optimum stimuli, 34
 Optogram, 842
 Ora serrata, 806, 831
 Orbicularis palpebrarum muscle, 807
 Organ of Corti, activation, 777
 function, 777
 structure, 775
 Orgasm, 1136
 Ornithin, 1084
 Osmatic animals, 690
 Osmometer, 1023
 Osmosis, 1023
 Osmotic pressure, 1024
 stimuli, 33
 Ossaceous canal of cochlea, 772
 labyrinth of ear, 771
 Ossicles, 764, 766
 movements, 767
 Otocyst, 781
 Otolithic cavity, 781
 Otoliths, 781
 Ovaries, 1129
 function, 981
 Overtones, fundamental, 759
 Ovists, 1117
 Ovulation, menstruation and, relation, 1133
 Ovum, 1117
 fertilization of, 1118
 implantation of, 1137
 migration of, 1135
 polar bodies of, 1118
 spermatozoa and, place of meeting, 1137
 Oxidase, 513
 Oxidations, hydrolytic, 511
 Oxidations of ferments, 991
 seat and nature, 508
 Oxidative glycosuria, 966
 power of tissues, 508
 Oxidizing enzymes, 989
 Oxygen, activation of, theories, 511
 and hemoglobin, compounds of, properties, 185
 deficiency, effects of, 519
 diminution in partial pressure, effect on respiratory quotient, 517
 electronegative, 510
 in blood, condition of, 502
 increase in partial pressure, effect on respiratory quotient, 517
 ingo in starvation, 1053
 requirement of fetus, 1142
 respiratory, 445
 Oxyhemoglobin, 183
 preparation and quantity, 184
 spectrum of, 193
 Oxyntic cells of gastric glands, 920
 Ozone-autozone theory of activation of oxygen, 511
 PACINIAN corpuscles, 734
 Pace-maker, 315
 of peristalsis, 1015
 Pain, sense, 734, 740
 Pains, labor, 1144
 Pale muscle, 44
 Pallium, 665
 Palmitin of milk, 902
 Palpation method of recording arterial blood pressure, 366
 Palsy, diver's, 522
 Pancreas, 932, 951, 965
 histological changes in cells of, during secretion, 933
 internal secretion of, function, 966
 removal of, 965
 vasomotor nerves of, 438
 Pancreatic duct, 932
 glycosuria, 966, 1043
 juice, amylolytic action, 996
 character of, 935
 enzymes of, 935
 function, 995
 lipolytic action, 996
 methods of procuring, 933
 milk-curdling power, 996
 proteolytic power, 995
 secretion, regulation of, 935
 secretions, 918
 Papillary muscles, 267
 Parabiosis, 1116
 Paraglobulin, 170, 171
 Paragraphia, 698
 Paralytic secretion of saliva, 911
 Paraphasia, 694
 Parasympathetic system, 631
 Parathyroid glands, 951, 954
 extirpation, 955
 symptoms from, 956
 function, 961

- Parathyroid glands, position, 955
 structure, 955
 Parhormones, 953
 Parietal cells of gastric glands, 920
 pleura, 455
 Parotid salivary glands, 908
 Pars intermedia, 977
 Parthenogenesis, 1117, 1119
 artificial, 1119
 Parturition, 1144
 Passive immunity, 246
 motion, 36
 Patellar reflex, 599
 nature, 599
 Peduncle, inferior, of cerebellum, 710
 middle, of cerebellum, 709
 superior, of cerebellum, 709
 Pendular motion of small intestine, 1014
 Penis, 1127
 erection of, 1127
 Pepsin, 924
 Peptonization, effect of, on coagulation
 of blood, 224
 Perception reflexes, 592
 Percussion, 476
 Perhydridase, 513
 Pericardial fluid, 237, 263
 sac, 255
 Pericardium, function, 264
 Perilymph, 771
 Perimeter, 851
 Perimetry, 851
 Perimysium, 43
 Perineurium, 111
 Periodic reflexes, 592
 Periosteal reflexes, 599
 Peristalsis, myogenic theory, 1016
 neurogenic theory, 1016
 pacemaker of, 1015
 Peristaltic wave, 1014
 regular, 1014
 Peritoneal cavity, absorption from,
 1033
 Pernicious anemia, 905
 Peroxidase, 513
 Pfeffer's experiment in phagocytosis,
 204
 Pflüger's aërotonometer, 490, 491
 law of contraction, 146, 148, 149
 theory of sleep, 724
 Phagocytes, 204
 Phagocytosis, 203
 Pfeffer's experiment, 204
 in immunity, 247
 Pharyngeal reflex, 598
 thirst, 755
 tonsils, 907
 Phenomenon of Purkinje, 880
 Phlebogram, 388
 Phloridzin glycosuria, 1043
 Phonating organs, general arrangement,
 540
 Phonation, 549
 Phosphates in urine, 1082
 Phosphatides, 25
 Phosphenes, 844
 Phospholipin, 217
 Phospholipins of bile, 948
 Photic stimuli, 33
 Photo-hemotachometer, Cybulski's, 405
 Phylloporphyrin, 189
 Physiology, definition, 17
 history of science, 18
 scope, 17
 Pia mater, 716
 Piéron's theory of sleep, 724
 Pigments, muscle, 87
 Pilocarpin, effect of, on salivary secre-
 tion, 916
 Pineal gland, 980
 position and function, 980
 Pinna, 763
 Pitch of sounds, 758
 Pithing, 530
 Pitot's tubes, 405
 Pituitary gland, 977
 anterior lobe, function of, 979
 position, 977
 posterior lobe, function of, 978
 removal of, effects, 977
 structure, 977
 Pituitrin, 978
 effect on mammary gland, 979
 on uterus, 978
 Placenta, 1140
 development, 1140
 function, 1141
 interchange of gases in, 451
 Plane mirror, reflection from, 796
 Plano-concave lens, 800
 Plano-convex lens, 800
 Plantar reflex, 599
 Plasma of blood, 159
 corpuscles and, relative amount, 159
 salted, 223
 Plasmozym, 215
 Plate, refraction by, 799
 Platelets, blood, 159, 207, 208, 214.
 See also *Blood platelets*.
 Plethora, hydremic, 1074
 Plethysmograph, air, Schäfer's, 398
 detection of vasomotor action by, 420
 glass, 400
 Mosso's, for arm, 399
 Plethysmographic method of estimating
 blood supply, 398
 Pleura, 455
 parietal, 455
 visceral, 455
 Pleural cavity, complementary, 462
 Pleurisy, 457
 Plexus cardiacus, 310
 gastricus anterior, 434
 posterior, 434
 ventralis, 434
 hepatic, 939
 nerve, 112
 renalis, 435
 solaris, 434
 suprarenalis, 434, 968

- Plica semilunaris, 808
 Pneumatogram, 473
 Pneumatograph, Gad's, 480
 Pneumogastric nerve, 654. See also *Vagus nerve*.
 Pneumograph, Marey's, 473
 Pneumonia, 477
 Pneumothorax, 457
 Pohl's commutator, 61
 pole changer, 61
 Poikilocytes, 175, 176
 Poikilothermal animals, 1093
 Poiseuille's manometer, 293
 Poisons, snake, effect of, on coagulation
 of blood, 225
 Polar bodies of ovum, 1118
 Polarization current, reaction of nerve
 to, 142
 external, 143
 in voltaic cell, 58
 internal, 143
 Polarizing current, 144
 Pole-changer, Pohl's, 61
 Policemen of blood, 204
 Pollutions, seminal, 1129
 Polycythemia, 163, 180
 Polymorphonuclear leukocytes, 200
 Polynuclear leukocytes, 200
 Polypnea, 525
 heat, 1095
 Pomum, Adami, 542
 Portal circuit of circulatory system, 259
 circulation, 433
 vein, 259
 Porus opticus, 834
 Position, change of, effect on arterial
 blood pressure, 372
 sense of, 781
 Post-anelectrotonus, 144
 Post-catelectrotonus, 144
 Posterolateral tract, 613
 Posteromedian tract, 613
 Potassium in nerve, 115
 theory of cardiac inhibition, 320
 Precipitins, 248
 Preformation theory of reproduction,
 1117
 Pregnancy, 1138
 effect of, on arterial blood pressure,
 371
 on general health, 1139
 mammary glands in, 898, 1138
 signs of, 1138
 uterus at end of, 1138
 uterus during, 1138, 1139
 vomiting of, 1139
 Premenstruation, 1133
 Prepuce, 1127
 Prepyramidal tract, 616
 Presbyopia, 830, 855
 Press, abdominal, 479, 531, 1011
 in labor, 1145
 in micturition, 1077
 Pressure, diffusion, 446
 head-, 350
 Pressure, intra-abdominal, changes in,
 478
 intracranial, 441
 intra-ocular, 805, 810
 intrapleural, 457
 intrapulmonic, 457
 changes in, 478
 intrathoracic, 457
 cause of negativity, 460
 changes in, 477
 lateral or side, 349
 osmotic, 1024
 resistance-, 350
 sense, 734
 sources, 347
 velocity-, 350
 Preyer's chemical theory of sleep, 724
 Priapismus, 1128
 Primitive sheath of nerve, 111
 Primordial follicles, 1129
 Prism, refraction by, 799
 Prismatic spectrum, 879
 Prochymosin, 925
 Pro-estrus, 1133
 Proferment, 215, 990
 Projection system of cerebrum, 660
 Prophase of mitosis of cell, 1111
 Proprioceptors, 730
 Prorennin, 925
 Prosecretin, 936
 Prosencephalon, 664
 Prostate gland, 1126
 Protease, 513
 Proteins, 26
 absorption of, 1031
 circulating, 1048
 diffusion of, 1026
 endogenous, 1049
 exogenous, 1049
 metabolism of, 1048
 end-products of, 1050
 of body, source, 1048
 of milk, 903
 of muscle, 85
 of muscle-plasma, 86
 of muscle-stroma, 86
 of nerve, 114
 reaction of intestinal bacteria on, 998
 specific dynamic action, 1059
 in metabolism, 1059
 tissue-, 1048
 utilization, 1049
 Proteolytic-enzyme of saliva, 994
 enzymes, 989
 property of pancreatic juice, 995
 Prothrombin, 213, 215
 Protocerebrum of crayfish, 580
 Protoplasm, 22
 alternate contraction and expansion,
 38
 conductivity, 35
 contractility, 35
 irritability of, 35
 of cell, 21
 theories of structure, 24

- Pseudoglobulin, 172
 Pseudonucleoli of cell, 25
 Pseudopodia, 203
 Pseudo-reflexes, 637
 Psychic blindness, 688
 feeding for study of gastric juice, 930
 Psycho-auditory region, 689
 Psychophysical law of Fechner, 733
 Psychovisual region, 684
 Ptyalin, 909, 988
 action of, 993
 Ptyalinogen, 909
 Puberty, 1125
 Pulmonary circuit of circulatory system, 260
 circulation, 430
 Pulmotor, 484
 Pulse, arterial, 377. See also *Arterial pulse*.
 pressure, 386
 venous, 388. See also *Venous pulse*.
 Pulsus alternans, 388
 bigeminus, 388
 celer, 387
 deficiens, 387
 durus, 387
 frequens, 387
 inequalis, 387
 intercurrents, 388
 intermittens, 387
 magnus, 387
 mollis, 387
 parvus, 387
 rarus, 387
 tardus, 387
 Punctum proximum of vision, 828
 remotum of vision, 828
 Puncture, lumbar, 720
 Pupil, constriction of, in anesthesia, 814
 dilation of, spinal center for, 596
 drugs constricting, 814
 dilating, 814
 Purin bodies, 1051
 bases in urine, 1087
 excretion in starvation, 1053
 of muscle, 87
 Purkinje, cells of, 560, 708
 figures or images, 839
 phenomenon, 880
 Purple, visual, 840. See also *Visual purple*.
 Pus-corpuscles, 201
 Pycnometer, 162
 Pylorus, movements of, 1005
 Pyramidal cells, 560
 spinal tracts, 615
 tract, 661
 Pyrexia, 1106

 QUINCKE'S method of determining quantity of blood, 228
 Quinquaud and Gréhan's method of determining quantity of blood, 227

 RACEMOSE glands, 892
 Radiating stimuli, 33
 Radiation, auditory, 661
 Radiolaria, 20
 Radiometer, resistance, 1099
 Rami viscerales, gray, 414
 white, 414
 Ramus albus communicans, 633
 griseus communicans, 633
 sacculo-ampullaris, 787
 utriculo-ampullaris, 787
 Ranvier's nodes, 113
 theory of muscular contraction, 50
 Rays, chemical, 880
 heat, 880
 Reaction, 575
 bimolecular, 992
 Erb's, 156
 galvanotropic, 789
 of blood, 164
 unimolecular, 992
 Reactions, paradoxical temperature, 743
 voluntary, 110
 Receptor substance of nerve, 116
 Receptors, 249
 cutaneous, structure, 734
 different types, 583
 somatic, 730
 visceral, 730
 Recessus utriculi, 483, 783
 Recording stromuhr, 396
 Red blood corpuscles, 172. See also *Blood corpuscles, red*.
 muscle, 44
 Red-blindness, 888
 Reflection from convex spherical mirror, 797
 from plane mirror, 796
 of light, 795
 Reflex action, 109, 583
 animal, 584
 cardiac death, 326
 center for defecation, 1019
 for micturition, 1077
 spinal cord as, 594
 circuits, 110
 joining of, 580
 of nervous system, 575
 concept of nervous system, 574
 croaking of frog, 588
 fatigue, 585
 regulation of respiration, 533
 scratching, 592
 spinal. See *Spinal reflex*.
 stimulus, subminimal, 585
 time, 585
 Reflexes, 110, 575
 accelerating and conditioning of, 591
 accommodation, 648, 812, 814
 alternating, 592
 antagonistic, 592
 association, 582, 592
 axon-, 637
 classification, 591

- Reflexes, clonic, 592
 complex, 592
 cremasteric, 592
 crossing, 586
 inhibition of, 588
 by afferent impulses, 589
 by midbrain, 589
 cerebral, 588
 from lessening irritability of nervous system, 590
 labyrinthine, 789
 light, 648, 812
 perception, 592
 periodic, 592
 pseudo-, 637
 simple, 591
 spastic, 592
 spreading, 586, 592
 threshold, 585
 tonic, 592
 trigeminus cardiac, 327
 yawning, 593
 Refraction, 798
 by biconcave lens, 803
 by biconvex lens, 800
 by plate, 799
 by prism, 799
 index of, 798
 of eye, abnormalities in, 853
 Refractive media, 799
 power of cornea, 809
 of crystalline lens, changes in, 827
 of eye, shadow test, 867
 tests for, 861
 Refractory period of heart beat, 341
 Regeneration, 1109, 1113
 of nerve, 122. See also *Nerve regeneration*.
 Regio olfactoria, 744
 respiratoria, 744
 Registers, vocal, 553
 Reissner's membrane, 775
 Relaxation period of muscular movement, 43
 Remak's ganglion, 318, 332
 Renal circulation, 433
 glycosuria, 966, 1043
 Rennet, 925
 Rennin, 901, 924
 Reproduction, 1109, 1116
 dynamic theories of, 1117
 of living substance, 32
 preformation theory, 1117
 sexual, 1117
 Reproductive organs, 1109, 1117
 female, 1122
 male, 1122
 Reptile heart, 257
 Repulsive odors, 747
 Residual air, 480
 blood, 229
 Resistance, 245
 Resonance of sounds, sympathetic, 761
 Resonant sounds, 554
 Resonator, Helmholtz's, 762
 König's, 762
 Respiration, 445
 abdominal type, 466
 accessory movements, 471
 action of intercostal muscles in, 468
 artificial, 482
 Calliano's method, 483
 for animals, 484
 mouth-to-mouth method, 484
 Sylvester's method, 483
 Biot, 524
 calorimeter, 1091
 changes in position of lungs in, 475
 chemical regulation of, 532
 chemistry of, 486
 Cheyne-Stokes, 523
 costal type, 466
 diaphragmatic, type, 466
 external, 447, 487
 in insects, 448
 in new-born infant, 460
 internal, 447, 487, 507
 nervous regulation of, 528
 number, 474
 of swallowing, 1002
 reflex regulation, 533
 self-regulation of, 538
 tissue, 507
 Respiratory capacity, 481
 center, cause of activity, 530
 location, 528
 nervous connections, 528
 regulation of activity, 531
 cycle, 455
 dynamic phase, 461
 function of diaphragm in, 462
 of ribs in, 465
 static phase, 456
 ferments, 513
 interchange, 514
 through skin, 450
 movements, 461
 character, 472
 frequency, 472
 mechanics of, 454
 methods of recording, 472
 modified, 481
 muscles, classification of, 471
 organs, special, 448
 oxygen, 445
 passage, upper, innervation of, 534
 pause, 456
 quotient, 514
 effect of composition of air on, 516
 of diminution in partial pressure of oxygen on, 517
 of external temperature on, 516
 of increase in partial pressure of oxygen on, 517
 of rate and depth of respiratory movements on, 516
 slight increase in partial pressure of carbon dioxide on, 518
 in hibernating animals, 515

- Respiratory quotient in sleep, 515
 - influence of sex on, 516
 - variations in, from character of food, 515
 - sounds, 476
 - variations in blood pressure, 486
 - Resistance-pressure, 350
 - Respired air, quantitative determination, 479
 - Resurrection plant, 37
 - Rete Malpighii, 893
 - testis, 1123
 - Retina, 806, 831
 - blind spot, 834
 - demonstration, 835
 - form of, 836
 - chemical and physical changes in, on stimulation by light, 840
 - corresponding points on, 873
 - general structure, 831
 - layers of, 831
 - rods and cones, 833
 - sensibility of, to colors, 884
 - yellow spot, 836
 - Retinal image, formation, 846, 848
 - inversion, 848
 - size, 850
 - Retinoscopy, 867
 - point of reversal in, 868
 - Retractor bulbi muscle, 870
 - lentic muscle, 821
 - Retzius, fiber cells of, 786
 - Reversibility of ferments, 991
 - Revolutio cordis, 272
 - Rheocord, 102
 - Rheoscopic frog preparation, 104, 105
 - Rhodopsin, 840. See also *Visual purple*.
 - Rhombencephalon, 664
 - Ribs, function of, in respiratory cycle, 465
 - Rigor, calcium, 337
 - caloris, 79
 - chemistry of, 93
 - mortis, chemistry of, 91
 - Rima glottidis, 543
 - palpebraris, 807
 - vocalis, 552
 - Ringer's solution, 182
 - effect on heart beat, 336
 - Ritter's tetanus, 146
 - Riva-Rocci's sphygmomanometer, 367
 - Rod-granules of retina, 832
 - Rods and cones of retina, 833
 - of Corti, 776
 - Rolando's substantia gelatinosa, 606
 - Roof ganglia of cerebellum, 708
 - Roots, hair-, 893
 - Rothe's rotatory apparatus for color discs, 881
 - Rubrospinal tract, 616
 - Russell and Brodie's method of estimating coagulation time of blood, 219
 - Sac, conjunctival, 807
 - dental, 1001
 - Sacculæ of ear, 771, 782
 - Sacral sympathetic system, 631
 - Saliva, 903
 - derivation of, 909
 - fat-splitting enzyme of, 994
 - function, 993
 - general character, 918
 - milk-curdling power of, 994
 - paralytic secretion, 911
 - proteolytic enzyme of, 994
 - Salivary corpuscles, 918
 - glands, 908
 - histological changes during activity, 910
 - character, 909
 - innervation of, 911
 - parotid, 908
 - sublingual, 908
 - submaxillary, 908
 - secretion, center for, 641
 - of adrenalin on, 916
 - of atropin on, 916
 - of ergotoxin on, 916
 - of nicotin on, 916
 - of pilocarpin on, 916
 - filtration theory of, facts disproving, 917
 - mechanism, 913
- Salivation, 911
- Salted blood plasma, 223
- Salts of milk, 902
- Sand, brain-, 981
- Santorini, duct of, 932
- Sarcolactic acid, 1041
- Sarcolemma, 44
- Sarcoplasm, 44
- Sarcostyles, 44
- Scala tympani, 772
 - vestibuli, 772
- Scapular reflex, 598
- Schäfer's air plethysmograph, 398
 - theory of muscle contraction, 50
 - of structure of protoplasm, 24
- Scheiner's accommodation experiment, 827
- Schlemm, canal of, 805
- Schönbein and Clausius' ozone-autozone theory of activation of oxygen, 511
- Schultze, comma tract of, 616
- Sciatic center, 595
 - nerve, vasomotor reaction, 421
- Sclera, 805
- Scrotal reflex, 598
- Scrotum, 1122
- Scurvy, cause, 927
- Sea-sickness, 790
- Sebaceous glands, 894
- Sebum, 895
- Second sight, 861
- Secretion, 936
 - gastric, 927
- Sécrétion externe, 951
 - interne, 951

- Secretion, histological changes in cells of
 pancreas during, 933
 movement by, 38
 of urine, 1064. See *Urine secretion*.
 skin as organ of, 894
- Secretions, 891
 chemical theory, 892
 classification, 889
 cutaneous, 889
 digestive, 908, 918, 938
 external, 889
 factors in formation of, 892
 filtration theory of, 892
 gastric, 918
 internal, 951. See also *Internal secretions*.
 lymphatic, 903
 mechanistic theory, 892
 mucous, 903
 pancreatic, 918
 vitalistic theory, 892
- Segmentation nucleus, 1119
- Semen, 1126
 ejaculation of, 1127
 pollutions, 1129
 spontaneous emissions, 1128
- Semicircular canals, 771, 785
 anterior or superior, 786
 effects of lesions of, 787
 of stimulation of, 788
 external or horizontal, 786
 posterior or inferior, 787
 relative position, 786
- Semilunar valves, 271
- Seminal vesicles, 1126
- Seminiferous tubules, 1123.
- Semivowels, sound production of, 554
- Sensations, olfactory, qualitative differences in, 747
 tactile, methods of evoking, 735
- Sense, dynamic, 730, 785
 of equilibrium, 781
 of hearing, 756
 of hunger, 743
 of movement, 785
 of pain, 734, 740
 of position, 781
 of pressure, 734
 of sight, 794
 of smell, 743
 of taste, 743
 topography of, 751
 of temperature, 734, 741
 of thirst, 743
 of touch, 734
 static, 578, 730, 781
- Sense-organs, 727
 adaptation of, 732
 classification, 727, 729
 fatigue of, 732
- Sensibilin, 252
- Sensitive plant, 37
- Sensitizing substance, 250
- Sensory aphasia, 696
- neuron, 109
- Sensory paralysis from hemisection of spinal cord, 626
- Septomarginal bundle, 616
- Sera, antitoxic, 246
- Serum, blood, 171, 212
 sickness, 251
- Serum-albumin, 170, 171, 172
- Serum-casein, 171
- Serum-globulin, 170, 171
- Sex, determination of, 1143
 effect of, on metabolism, 1054
 influence of, on respiratory quotient, 516
- Sexual glands, 982
 maturity, 1125
 organs, female, relation to mammary glands, 899
 reproduction, 1117
- Shadow test of refractive power of eye, 867
- Sham feeding for study of gastric juice, 930
- Shingles, 622
- Shivering, 1098
- Shock, 589
 theories of, 590
- Sickness, mountain, 519
 serum, 251
- Side-chain theory of immunity, 249
- Sighing, 482
- Sight center, 684
 nerve of, 645
 second, 861
 sense of, 794
- Sigismund's theory of menstruation, 1134
- Sign, Argyll-Robertson, 813
- Singing, 553
 voice, range, 553
- Sino-auricular node, 277
- Sinospiral fibers of ventricles, 266
- Sinus of Valsalva, 272
 venosus, 255
- Skeletal muscle tissue, vasomotors of, 421
 musculature, 42
- Skiascopy, 867
- Skin, absorption through, 1034
 as organ of protection, 893
 of secretion, 894
 cold spots, 742
 respiratory interchange through, 450
 varnishing, effect on body temperature, 1105
 warm spots, 742
- Sleep, 716, 721
 adult requirement, 721
 anemia theory, 723
 changes in depth, 722
 chemical theories, 723
 effect of, on arterial blood pressure, 370
 on metabolism, 1054
 hypnotic, 724
 inhibition theory, 723

- Sleep, mechanical block theory, 723
 phenomena of, 722
 respiratory quotient in, 515
 theories of, 723
- Smegma preputii, 895
- Smell, center for, 690
 nerve of, 644
 sense of, 743
- Smith and Haldane's method of determining quantity of blood, 227
- Snake poisons, effect of, on coagulation of blood, 225
- Sneezing, 482
 center for, 641
- Snellen's test types, 861
- Sniffing, 482
- Snoring, 482
- Sobbing, 482
- Sodium chlorid, effect of, on muscle, 80
 in blood, 169
 citrate method of blood transfusion, 231
- Solar spectrum, 879
- Solution, hyperosmotic, 1025
 hypertonic, 1025
 hyposmotic, 1025
 hypotonic, 1025
 isosmotic, 1025
 isotonic, 1025
 Ringer's, 182
 Stokes's, 186
- Somachrome cells, 564
- Somatic cells, 1114
 hunger, 754
 receptors, 727, 730
- Sound, muscle, 69
 waves, cause, 756
 character, 756
 conduction by cranial bones, 779
 rate of speed, 757
 reinforcement and interference, 760
- Sounds, 757
 color, 759
 intensity, 758
 loudness, 758
 musical, 758
 pitch, 758
 quality, 759
 stamp, 759
 sympathetic vibration or resonance, 761
 timbre, 759
 tone, 758
 vocal. See *Vocal sounds*.
- Spaces of Fontana, 805
- Spastic reflexes, 592
- Spaying, effects of, 982
- Specific gravity, movement by changes in, 38
- Spectrophotometric method of determining hemoglobin, 190
- Spectroscope, 192, 193
- Spectroscopic analysis of hemoglobin and derivative compounds, 192
- Spectrum, absorption bands, 192
 Fraunhofer lines, 193
 of acid hematin, 195
 of carbon monoxid hemoglobin, 194
 of hematoporphyrin, 195
 of hemochromogen, 195
 of methemoglobin, 194
 of nitric oxid hemoglobin, 194
 of oxyhemoglobin, 193
 of reduced hemoglobin, 193
 solar, 879
- Speech, 540, 553
 center, 691
 location, 693
 circuit, 691
- Spermatids, 1124
- Spermatocytes, 1124
- Spermatogonia, 1124
- Spermatozoa, 1124, 1125
 development and character, 1124
 migration of, 1136
 ovum and, place of meeting, 1137
 rheotactic quality, 1136
 thigmotactic quality, 1136
- Spermatozoön, 1117
- Sperm-cell, 1117
- Spermin, 1126
 action of, 982
- Spherical aberration, 815
 mirror, 796
 center of curvature, 796
 concave, 796
 convex, 796
 reflection from, 797
 geometrical center, 796
 principal axis, 797
 focus, 797
 secondary axis, 797
- Sphincter antri pylori, 1005
 of Henle, 1128
- urethræ membranaceæ, 1128
- Sphygmogram, 383
 clinical significance, 387
- Sphygmograph, Dudgeon's, 382
 Marey's, 382
- Sphygmography, 381
- Sphygmomanometer, Janeway's, 369
 Riva-Rocci's, 367
 von Basch, 366
- Spinal conduction, localization of, methods used for, 609
- Spinal cord as conducting path, 603
 as reflex center, 594
 automatic activity, 597
 centers, 596
 fasciculi, classification, 612
 function, 594, 622
 general structure, 603
 gray matter, functional basis, 606
 hemisection, effects of, 626
 posterior roots, distribution of impulses from, 623
 roots, function of, 519
 tracts, 610
 ascending, 616

- Spinal cord tracts, classification, 614
 descending, 615
 posterior, 616
 pyramidal, 615
 trophic function, 603, 621
 vasomotor reaction of, 421
 white matter, functional basis, 608
 reflex, abdominal, 598
 achillis jerk, 599
 bulbocavernosus, 599
 centers, localization, 594
 cremasteric, 598
 gluteal, 598
 jaw jerk, 599
 mammary, 598
 patellar, 599
 plantar, 599
 pharyngeal, 598
 scapular, 598
 scrotal, 598
 sternal, 598
 tensor tympani, 599
 winking, 599
 wrist jerk, 599
 reflexes, abolition, 601
 deep, 598
 exaggeration, 601
 from facial muscles, 599
 in mammals, 595
 organic, 598
 periosteal, 599
 reinforcement, 600
 superficial, 598
 Spinocerebellar tract, 617
 Spinotectal tract, 681
 Spinothalamic tract, 618
 Spindles, muscle, function, 784
 Spiral ganglion, 777
 Spirometer, Hutchinson's, 479
 Wintrich's modification, 479
 Splanchnic nerve, greater, vasomotor
 reaction of, 425
 nerves, function, 434
 system, 435
 Splanchnic minores, 435
 Spleen, 903
 disintegration of red corpuscles by,
 198
 formation of white blood corpuscles
 by, 904
 function, 904
 hematopoietic function, 905
 pulp of, 905
 removal of, effects, 904
 transplantation, 904
 vasomotor nerves of, 438
 Splenic artery, 433
 oncometer, 398
 Sponges, circulatory system in, 254
 Spongioplasm, 24
 Spontaneity of life, 33
 Spontaneous emission of semen, 1128
 Spot, blind, 834
 demonstration of, 835
 form of, 836
 Spot, germinal, 1130
 yellow, 836
 Squint, 873
 Stannius' experiment on heart beat, 333
 Stapedius muscle, 765
 Stapes, 767
 Starling's theory of formation of lymph,
 238
 Starvation, carbon dioxide in, 1053
 effect of, 1052
 elimination of nitrogen in, 1053
 oxygen in, 1053
 premortal rise in excretion of nitrogen
 in, 1053
 purin excretion in, 1053
 relation of sulphur to nitrogen in,
 1053
 urea nitrogen in, 1053
 Static phase of respiratory cycle, 456
 sense, 578, 730, 781
 Stationary air, 481
 Statocyst, 781
 Statolith, 781
 Steapsin, 935, 996
 Stearin of milk, 902
 Stellate cells of Kupffer, 939
 Stercobilin, 196, 1080
 Stercorubin, 948
 Stereoscope, 876
 Sternal reflex, 598
 Sternzellen of Kupfer, 198, 207
 Stethograph, 473
 Stethoscope, Laennec, 757
 Stewart's method of estimating circula-
 tion time, 410
 of measuring volume of blood
 stream, 397
 Stigma, 1130
 Stigmæ, 448
 Stimulants, alcoholic, 1063
 in diet, 1062
 Stimulation, futurity, 34
 phenomena of, 33
 threshold of, 34
 Stimuli, adaptation state, 35
 chemical, 33
 electric, 35
 maximal, 34
 mechanical, 33
 minimal, 34
 optimum, 34
 osmotic, 33
 photoc, 33
 radiating, 33
 refractory state, 35
 strength of, 34
 subminimal, 34
 thermal, 33
 Stirrup bone of ear, 767
 Stokes' solution, 186
 Stomach, antrum pylori, 1006
 bismuth x-ray study of, 1008
 contents, evacuation of, 1009
 time of, 1009
 fundus, 1006

- Stomach fundus, movements of, 1005
 layer of circular muscle strands, 1005
 movements of, 1005
 musculature, innervation of, 1012
 outer longitudinal muscular layer, 1006
 pyloric portion, 1006
 resistance of, to gastric ferments, 925
 teeth, 1001
 vasomotor nerves of, 438
 Strabismus, 873
 Striated muscle, 42
 action in locomotion, 46
 String galvanometer, Einthoven's, 286
 for measuring speed of nerve conduction, 130
 Stroma and hemoglobin of red corpuscles, separation, 181
 muscle, 85
 Stromuhr, detection of vasomotor action by, 420
 Ludwig's, 395
 recording, 396
 Subarachnoid system, 717
 Subarachnoid space, 716
 Sublingual salivary glands, 908
 Submaxillary salivary glands, 908
 Subminima' stimuli, 34
 Substance, living, 17
 Substantia gelatinosa, 605
 of Rolando, 606
 Substrate, 987
 Succus entericus, 949
 Sucking, center for, 641
 Sugar content of blood, 169
 of milk, 902
 supply of body, regulation of, 1042
 utilization of, 1040
 Suleus primarius of cerebellum, 706
 Sulphates in urine, 1082
 Sulphur, relation to nitrogen, in starvation, 1053
 Sunlight, speed of, 795
 Supplemental air, 480
 Supraglottic cavity, 544
 Suprarenal bodies, vasomotors of, 435
 capsules, 967. See also *Adrenal glands*.
 plexus, 968
 Suspensory ligament of eye, 821
 Swallowing, 998, 1001. See also *Deglutition*.
 respiration of, 1002
 Sweat, 896
 quantity secreted, 896
 Sweat-glands, 895
 innervation of, 897
 Swim-bladder of fish, 450
 Sylvester's method of artificial respiration, 483
 Sympathetic system, 627
 Synapse, 110
 Synovial fluid, 237
 Systemic circuit of circulatory system, 259
 Systole as period of decomposition, 341
 auricular, position of heart valves in, 307
 interpolated, 343
 ventricular, position of heart valves in, 307
 Systolic pressure, intracardiac, 296
 TACTILE acuity, 736
 agnosia, 684, 697
 discrimination, 625, 736
 localization, 625, 736
 sensations, methods of evoking, 735
 Talking dog, 692
 Tallquist's method of estimating hemoglobin, 191
 Tambour, Marey's, 285
 Taste buds, activation of, 750
 innervation of, 749
 power of reaction, 751
 structure, 748
 center, 691
 sense of, 743
 topography of, 751
 Taste-pore, 748
 Taurin, 87
 Taurocholic acid, 947
 Tea, 1063
 Tectorial membrane, 777
 Tectospinal bundle, anterior, 616
 Teeth, eye, 1001
 milk, 1001
 permanent, 1001
 stomach, 1001
 wisdom, 1001
 Teichmann's hemin crystals, 188
 Telophase of mitosis of cell, 1112
 Temperature, effect of, on metabolism, 1054
 on muscle contraction, 78
 on speed of nerve conduction, 132
 external, effect of, on respiratory quotient, 516
 of blood, 162
 of body, 1093. See also *Body temperature*.
 reactions, paradoxical, 743
 sense of, 734, 741
 Temporopontine fibers, 661
 Tendril fibers of cerebellum, 708
 Tenon's capsule, 804, 869
 Tensor tympani muscle, 765
 reflex, 599
 Tentorium cerebelli, 716
 Test breakfast, 923
 tube, living, 222
 types, Snellen's, 861
 Testes, function, 982
 Testicles, 1122
 Tetania parathyreopriva, 962
 Tetanic current, 62
 Tetanus, 71, 72
 incomplete, 71
 of nerve, secondary, 148
 Ritter's, 146

- Tetanus, secondary, 104
 Wendt's, 146
 Tethelin, 980
 Thalamocortical tract, 660
 Thalamus opticus, 703
 Thebesius foramina of, 428
 Theca folliculi, 1130
 Theine, 1063
 Theobromine, 1062
 Theorem of Toricelli, 348
 Thermal stimuli, 33
 theory of light stimulation of retina, 840
 Thermodynamic theory of muscle contraction, 49
 Thermogenesis, 1092, 1097
 Thermolysis, 1099
 Thermometry, 1089
 Thermostat, 1097
 nervous mechanism regulating, 1102
 Thiery's method of obtaining intestinal juice, 949
 Thirst, 754
 general, 755
 pharyngeal, 755
 sense, 743
 Thoma-Zeiss hemocytometer, 176
 Thoracic duct, 234
 sympathetic nerve, 434
 system, 631
 Thorax, aspiratory power of, 464
 Threshold contraction of muscle, 76
 substances, 1073
 Thrombin, 213, 215
 Thrombocytes, 159, 207, 208, 214
 Thrombogen, 170, 172, 213, 215
 Thrombokinas, 210, 213, 214
 Thromboplastic substance, 222
 Thymus gland, 951, 963
 extirpation of, effects, 964
 function, 964
 position, 963
 structure, 963
 Thyro-arytenoid muscle, 547
 Thyroid cartilage, 542
 gland, 951, 954
 active principle, nature of, 960
 extirpation, 955
 symptoms from, 956
 function, 961
 guanidin metabolism in, 963
 position, 954
 structure, 954
 Thyroidin, 960
 Thyro-oxy-indol, 960
 Thyroxin, 960
 Tidal air, 480
 blood and, interchange of gases between, 488
 Tigroid bodies, 563, 564
 Timbre of sounds, 759
 Time, reflex, 585
 Tissue nucleoproteid, 222
 oxidative power, 508
 respiration, 507
 Tissue, thirst, 755
 Tissue-fibrinogen, 222
 Tissue-fluid, 233
 reactions of, 248
 Tissue-protein, 1048
 Toisson's fluid, 177
 Tones, fundamental, 759
 Tonic contracture of muscle, 75
 reflexes, 592
 Tonicity of muscle, 66
 of smooth muscle, 83
 Tonsils, 906
 faucial, crypts of, 906
 function, 906
 removal of, effects, 907
 pharyngeal, 907
 Tonus, labyrinthine, 789
 Töpler's pump for extraction of gases from blood, Barcroft modification, 499
 Toricelli's theorem, 348
 Tormina intestinum, 1019
 Touch areas, 739
 illusions, 739
 sense, 734
 Toxogenic theory of fever, 1107
 Toxogenin, 252
 Toxophore, 249
 Trachea, 452, 455
 Tract, anterolateral superficial, 618
 comma, of Schultze, 616
 direct, 617
 Flechsig's, 617
 Gower's, 613, 618
 olfactory, 644
 olivospinal, 616
 posterolateral, 613
 posteromedian, 613
 prepyramidal, 616
 pyramidal, 661
 rubrospinal, 616
 spinocerebellar, 617
 spinotectal, 618
 spinothalamic, 618
 thalamocortical, 660
 vestibulospinal, 616
 Tracts of cerebrum, classification, 659
 of spinal cord, 610
 classification, 614
 Transfusion of blood, 230
 Translucent bodies, 795
 Transparent media, 795
 Traube-Hering curves, 364, 393
 Traube's theory of activation of oxygen, 512
 Traumatic epilepsy, 677
 Tremors from cerebellar disease, 713
 Treppe phenomenon of muscle fatigue, 90
 Tricuspid valve, 268
 Trigemini cardiac reflex, 327
 nerve, 534, 649
 vasomotor reaction of, 422
 Tritocerebron of crayfish, 580
 Trochlear nerve, 649

- Trophic state of muscle, 67
 theory of cardiac inhibition, 319
 Trypsin, 935
 Tubular glands, 892
 Tubulo-racemose glands, 892
 Tunica albuginea, 1123, 1127
 externa, 415
 media, 415
 Tunnel of Corti, 776
 Türk's column, 612
 Türk's mixture for counting white blood corpuscles, 201
 Tweenbrain, 664
 Tympanic membrane, 764, 765
 Tympanum, 763, 764
 Tyrosinase, 513, 514
- UMBILICAL artery, 260
 cord, 142
 vein, 260
 Uncinate fasciculus, 661
 Undulatory theory of light, 794
 Unimolecular reaction, 992
 Unipolar stimulation of muscle and nerve, 151
 effects of, 154
 Upper extremity, motor points in, 152
 Urea, 1051
 content of blood, 170
 daily excretion of, 1085
 in urine, 1083
 nitrogen in starvation, 1053
 origin of, in liver, 1084
 Uremia, 1084
 Ureters, 1076
 Urethra, 1123
 Urethral glands, 1126
 Uric acid in urine, 1087
 Urinary bladder, 1076
 nervous control, 1077
 tubules, absorption of water from, in urine secretion, 1071
 Urine, 1080
 acetone in, 1086
 amino-acids in, 1087
 ammonia in, 1086
 carbamide in, 1083
 carbonates in, 1082
 chlorids in, 1081
 color, 1080
 composition, 1080, 1081
 creatin in, 1087
 creatinin in, 1087
 freezing point, 1081
 general characteristics, 1080
 hippuric acid in, 1087
 indican in, 1082
 indole in, 1082
 inorganic constituents, 1081
 odor, 1080
 organic constituents, 1083
 phosphates in, 1082
 purine bases in, 1087
 quantity, 1080
 reaction, 1081
- Urine, regurgitation of, prevention, 1076
 secretion of, 1064
 absorption of water from urinary tubules in, 1071
 Ludwig's filtration theory, 1067
 modern theory, 1072
 pure mechanical theory, facts contradicting, 1068
 stimulation of, 107
 theories of, 1067
 specific gravity, 1080
 sulphates in, 1082
 taste, 1080
 urea in, 1083
 uric acid in, 1087
 viscosity, 1081
 Urobiligen, 948
 Urobilin, 196, 948, 1080
 Urobilinogen, 1080
 Urochrome, 196, 1080
 Uroerythrin, 1080
 Uterus at end of pregnancy, 1138
 contraction of, spinal center for, 596
 effect of pituitrin on, 978
 in pregnancy, 1138, 1139
 virgin, 1138
 Utricle of ear, 771, 782
- VAGI nerves, function, 434
 Vagus nerve, 654
 divided, excitation of central end, 537
 stimulation of distal end, 537
 function of, 536
 inferior laryngeal branches, 535
 pressure on, effect on heart, 327
 specificity of, 316
 superior laryngeal branch of, 534
 Valsalva, sinus of, 272
 Valve, Eustachian, 262
 ileocecal, 1017
 Valves, auriculoventricular, 268
 of heart, 263
 arrangement, 267
 play of, 306
 semilunar, 271
 van't Hoff's theory of activation of oxygen, 511
 Vas deferens, 1123
 Vasa efferentia, 1123
 recta, 1123
 Vascular system, general arrangement, 253
 Vasoconstriction, 412
 theories of, 417
 Vasoconstrictors, 412
 Vasodilatation, 412
 theories of, 417
 Vasodilators, 412
 Vasomotor action, methods of detecting, 420
 center, 412
 activity of, 413
 location of, 412

- Vasomotor fibers, distribution of, 414
 nerves of intestines, 437
 of kidneys, 435
 of liver, 438
 of pancreas, 438
 of spleen, 438
 of stomach, 438
 of suprarenal bodies, 435
 reaction, nature of, 417
 of cervical sympathetic nerve, 422
 of depressor nerve, 427
 of greater splanchnic nerve, 425
 of sciatic nerve, 421
 of spinal cord, 421
 of trigeminus nerve, 422
 results, 418
 Vein, umbilical, 260
 Veins, 254
 Velocity-pressure, 350
 Vena cava, 254
 gastrolialalis, 433
 pancreatica, 433, 933
 Venæ mesentericæ, 433
 Venous blood pressure, 373. See also
 Blood pressure, venous.
 pulse, 388
 pathological, 390
 physiological, 388
 speed and character, 389
 Ventilation, 526
 negative, 539
 positive, 539
 Ventricle, fourth, 663
 Ventricles, bulbospiral fibers, 266
 circular fibers of, 267
 discharging period, 307
 function, 300, 302
 musculature of, 265
 of heart, 255
 of Morgagni, 545
 period of filling, 308
 setting period, 308
 sinospiral fibers, 266
 structure, 263
 Ventricular complex of electrocardio-
 gram, 288
 fibrillation, 279
 systole, position of heart valves in, 307
 Venules, 254
 Veratrin, effect of, on muscle, 79
 Vermes, circulatory system of, 255
 Vermis, inferior, of cerebellum, 706
 median, of cerebellum, 706
 superior, of cerebellum, 706
 Vernix caseosa, function, 895
 Vertebrates, circulatory system in, 256
 Verworn's theory of muscle contraction,
 50
 Vesicles, seminal, 1126
 Vestibular membrane, 775
 Vestibule, aortic, 267
 Vestibulospinal tract, 616
 v. Helmholtz's method of determining
 speed of nerve conduction, 129
 Vibration sympathetic, of sounds, 761
 Vibratory energy, 728
 Vierordt method of estimating coagula-
 tion time of blood, 219
 Vierordt and Glan's method of deter-
 mining hemoglobin, 190
 Virgin uterus, 1138
 Virtual focus, 798
 image, 798
 Visceral musculature, 42
 nervous system, 627
 pleura, 455
 receptors, 727, 730
 Viscosimeter, 167
 Viscosity of blood, 166
 variation, 167
 of urine, 1081
 Vision. See *Sight.*
 binocular, 869, 872
 color, 879. See also *Color vision.*
 direct, 837
 electrical variations in eye on, 844
 far-point of, 828
 indirect, 837
 near-point of, 828
 Visual acuity, 838
 after-effects, 882
 agnosia, 697
 association, 686
 axis of eye, 837
 axes of eye, secondary, 837
 center, connection with other centers,
 687
 field, 851
 judgment, 874
 purple, 840
 bleaching property, 842
 extraction of, 842
 function, 843
 white, 843
 yellow, 843
 Vital capacity, 481
 Vitalism, 238, 893
 Vitalistic theory of secretion, 892
 Vitamines, 926
 Vitreous humor, 810
 Vividiffusion, 1049
 v. Kries apparatus for recording capil-
 lary blood pressure, 376
 Vocal aperture, 552
 cords, 540, 543, 550
 approximation of, 546
 false, 543
 true, 543
 tension, 545
 registers, 553
 sounds, characteristics, 551
 dental, 554
 explosive, 554
 friction, 554
 guttural, 554
 labial, 554
 linguopalatal, 554
 loudness, 552
 nasal, 554
 peculiarities, 553

- Vocal sounds, pitch, 552
 production of, 551
 quality, 552
 resonant, 554
- Voice, 540
 breaking of, 552
 chest, 551
 falsetto, 551
 singing, range, 553
- Volkman's hemodromometer, 404
- Voltaic cell, polarization in, 58
- Voluntary muscle contraction, 73
 reactions, 110
- Vomiting, 1011
 center for, 641, 1012
 of pregnancy, 1139
- von Basch sphygmomanometer, 366
- Vowels, sound production of, 554
- WALDEYER's neuron doctrine of nervous system, 565
 arguments in favor, 567
- Waller's ergograph or dynamograph, 81, 82
 law of nerve degeneration, 119, 621
- Warm spots of skin, 742
- Water, absorption of, 1027
 from urinary tubules in urine secretion, 1071
 calorimeter, 1090
- Water-rigor of muscle, 93
- Wave, antiperistaltic, 1014
 peristaltic, 1014
 regular, 1014
 theory of nerve conduction, 133
- Weber's law, 733
 theory of muscle contraction, 49
- Welker's method of determining quantity of blood, 226
- Welker and Hoppe-Seyler's chronometric method of determining hemoglobin, 190
- Wendt's tetanus, 146
- Wernicke's sensory aphasia, 696
- Whartonian jelly, 1142
- Whey, 901
- Whispering, 553
- White blood corpuscles, 199. See also *Blood corpuscles, white.*
 light, 879
 matter, cerebral, general arrangement, 658
 of spinal cord, functional basis, 608
 of eye, 805
 visual, 843
- Winking reflex, 599
- Wintrich's modification of Hutchinson's spirometer, 479
- Wirsung, duct of, 932
- Wisdom teeth, 1001
- Word-blindness, 688, 696
- Word-deafness, 688, 689
- Work-adder, diagram of, 96
- Wrist jerk, 599
- XANTHIN, 1051
- Xanthinoxidase, 513
- X-ray bismuth study of stomach, 1008
- YAWNING, 482
 reflex, 593
- Yellow spot, 836
 visual, 843
- Young-Helmholtz theory of color vision, 886
- ZÖLLNER's lines, 878, 879
- Zona pellucida, 1130
- Zuntz's indirect method of determining cardiac output, 302
- Zwaardemaker's olfactometer, 745
- Zymase, 988
- Zymogen, 990
 granules, 909
- Zymoplastic substance, 222

UNIVERSITY OF CALIFORNIA
MEDICAL CENTER LIBRARY

**THIS BOOK IS DUE ON THE LAST DATE
STAMPED BELOW**

Books not returned on time are subject to a fine of 50c per volume after the third day overdue, increasing to \$1.00 per volume after the sixth day. Books not in demand may be renewed if application is made before expiration of loan period.

JUN 10 1946

MAR 13 1947

MAR 13 1947

APR 10 1947

APR 13 1951

QP34	Burton-Opitz, R.	49342
B967	A text-book of physiology.	
192D		

K. Gonzalez	JUN 10 1946	MAY 31 1946
M. Jordan	MAR 13 1947	MAR 10 1947
M. Jordan	APR 13 1951	APR 10 1951
J. Strain		APR 12 1951

49342

SCHOOL LIBRARY