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Comparative Physiology of
Vertebrate Respiration

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COMPARATIVE PHYSIOLOGY OF Vertebrate Respiration

by

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To my mother and father

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Preface

In the past it has generally been true that studies in comparative physiology have been made either by Mammalian Physiologists interested to find convenient animals in which to investigate particular physiological mechanisms, or by Zoologists wishing to extend their knowledge of animal structure, evolution, and adaptation by investigating function. Nowadays increasing numbers of biologists learn both Physiology and Zoology and hence the synthesis of these two approaches has become increasingly common at the university level and is rapidly becoming more important in school biology teaching. As a consequence such borderline subjects as 'Physiological Ecology' and 'Physiological Genetics' have come into being, but 'Functional Morphology' remains a basic element. In its broadest context this involves a knowledge of classical comparative anatomy, ecology, evolution, physiology and biochemistry. The amalgamation of parts from all these disciplines is an enormous task but it is one in which Zoologists hold a central position. It is hoped that this small book will indicate the nature of such a broad-based approach in which the focal point remains the animal in its environment and its evolution.

One general feature of the comparative approach—to anatomy or physiology—is that it is based upon a serial consideration of individual organ systems. This sometimes gives rise to the misconception that physiologists are concerned only with parts of living organisms. But nothing could be further from the truth, for a diagnostic character of the physiological approach is the stress on integration, not only within each functional system but between them.

The aspect of vertebrate physiology dealt with in this book is ideal for illustrating a corollary of this—that the study of a given system needs to take into account the function of many other systems. Respiration involves a consideration of the animal's environment as a source of oxygen as well as the biochemistry of the cell. From the evolutionary point of view the major structural and physiological changes are dominated by the origin of the land habit which has profoundly affected both the respiratory and circulatory systems.

Many aspects of physiology considered here are 'Homeostatic' in that they tend to maintain constant within limits some feature of the animal's internal environment, usually by some feedback mechanism. In a sense this book also represents a 'feedback' because my interest in the respiratory physiology of fishes arose from demonstrating to Professor Sir James Gray's course at Cambridge. The stimulus to research in this field was a valuable one and I only hope that others may feel the desire to follow up some of the many gaps which exist in our knowledge.

In writing this book I have tried to include material which will be useful for 'S' level candidates in Zoology as well as introductory courses at universities. Recent views have been given in many instances and where they differ from common acceptance this has been noted. Some of the diagrams are new and it is hoped that they will summarise those parts of the text which they illustrate. Unfortunately errors are bound to be present for which I apologise both to the reader and to authors whose views I may have unwittingly misrepresented.

It is a pleasure to record my thanks to Mr W. H. Dowdeswell, the editor of *The Scholarship Series* not only for inviting me to write this book but for his very helpful comments on the typescript.

Magdalene College,
Cambridge
June 1962

G. M. HUGHES

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Three figures are taken directly from other publications and I am grateful to the following authors and publishers for permitting their use in this book: Professor G. E. H. Foxon and the Cambridge University Press for figures 30 and 31; Drs Dawes, Mott, Born, and Widdicombe, and the Long Island Biological Association for figure 37.

I also wish to thank the authors of publications from which some of the other figures have been redrawn. When the reference is not given in the legend it will be found in the 'Further Reading' section.

For his guidance through the diverse problems that have arisen during publication, it is a pleasure to thank Mr Hamish MacGibbon of Heinemann Educational Books Ltd.

I also wish to thank my wife for her help at all stages in the preparation of this book.

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G. M. H.

In this reprint an index of animals has been added and a number of alterations have been made to the text. For their advice on the amendments I am most grateful to a number of friends and colleagues, especially Dr G. S. Carter, Dr J. F. Mott and Dr J. A. Ramsay.

November 1964

G. M. H.

Introduction

The structure and organisation of vertebrates are extremely complex whether considered at the gross level of the mechanics of the skeletal and muscular systems or at the cellular and molecular levels. Such complexity requires the expenditure of energy if it is to be maintained. Furthermore, energy is required for the performance of the normal activities of the organism. The energy for both of these processes is provided by the degradation of large molecules and ultimately depends on oxidative reactions in the cells. The provision of the oxygen and hence the energy for the vital processes of the organism is the fundamental contribution which respiration makes to the physiology of all living organisms. Although these cellular oxidative processes are of basic importance, they cannot take place in animals the size of vertebrates in the absence of mechanisms which enable oxygen to be transferred from the external medium to the cells. The first of these, involving the intake of oxygen to the organism and the removal of carbon dioxide, is referred to as *external respiration*. Among vertebrates, many adaptations are found in the respiratory organs which enable this exchange to take place efficiently. These are partly due to the extent (Table 1) and nature of the surfaces which allow rapid diffusion to take place, but also include mechanisms for changing the medium at the epithelial surface in order to ensure a constant supply of oxygen. Diffusion processes are sufficient to account for the exchange at all respiratory surfaces although some early workers believed that oxygen was actively secreted into the blood in some respiratory organs.

Above a certain average diameter, diffusion is insufficiently

rapid to provide enough oxygen to meet the oxygen requirements of living organisms. All adult vertebrates come into this range and the supply of oxygen to the tissues following its absorption at the respiratory surface is maintained by a convection process involving circulation of the blood. The circulatory system forms the *transport mechanism* of the body and blood carries the oxygen partly in solution but mainly in combination with a respiratory carrier (haemoglobin) contained in the red blood corpuscles. There are one or two exceptions to this generalisation, however, because haemoglobin is completely absent from the bloods of certain vertebrates. The *Leptocephalus* larva of the eel is a well-known example which is transparent and contains no red pigment. The supply of oxygen is greatly facilitated by the thinness of these larvae and diffusion through the relatively large body surface plays an important part. Recently a whole group of fishes in the Antarctic has been shown to be completely devoid of haemoglobin although they live relatively normal lives. At the low temperatures of their marine environments the water contains a large percentage of oxygen and their metabolic rate is probably low. In addition to these 'ice-fish' several examples have been described in vertebrates of abnormal specimens containing no haemoglobin (e.g., the clawed toad *Xenopus*). All these animals without haemoglobin appear to lead fairly normal lives although they do not become highly active. It is probable that the presence of haemoglobin is essential for very active organisms but even when it is destroyed by combination with carbon monoxide many fishes, for example goldfish, are able to live for reasonable lengths of time so long as they are kept at low temperatures and remain inactive.

(a) THE OXYGEN REQUIREMENTS OF VERTEBRATES

The amount of oxygen used by animals varies according to many factors. Most important are their size, activity, and the temperature. The figures in Table 1 are representative of vertebrates when at rest. It is clear that the metabolic rate of birds and mammals is greater than that of lower vertebrates (see

TABLE I

<i>Animal</i>	<i>Lung or gill surface area sq. cms/grm</i>	<i>O₂ consumption (resting) ccs/kgm/hr °C</i>	<i>O₂ capacity of blood Vols %</i>	<i>Blood volume ml/kgm</i>
Dogfish	1.86	54.5 (15°)	5	70
Dragonet	2.0			
Trout	3.4	226 (15°)	13.8	25
Cod	ca. 4.5			
Mackerel	11.6	726 (20°)	16	
<i>Lepidosiren</i>	0.25	42 (20°)		
Frog	2.5	Wi 105 (20°) Su 211 (20°)	10	88
Salamander	0.67			
<i>Alligator</i>				
<i>Varanus</i>	1.0	74 (16°)	7	
Python	5.0	12.2 (22°)		
Humming Bird				
Pigeon		11,000	20	92
Crow	0.65	710 (41°)*	17	
Bat (little brown)	100	1500 (37°)*		78
Mouse (white)	54	3600 (37°)*		58
Rat (white)	33	770 (37°)*		
Seal	13	500 (37°)*	29.3	
Man	7	200 (37°)*	20	75

*External temperature 24°

Chapter 5). This is partly because they are warm-blooded and therefore the resting metabolism given is at a higher temperature than for the others. But even at the same body temperature, poikilothermic animals of the same size show a metabolic rate which is markedly lower than that of birds and mammals. This is also true when the oxygen consumption of mammals is measured with their body temperature lowered (e.g., a man under hypothermia). Despite these variations and those due to body size, it is clear that the range of resting metabolic rates found among vertebrates is not as great as might be imagined when one considers the wide range in their structure and mode of life. There are, of course, wide extremes such as humming birds which require more than 10,000 ccs of oxygen per kilogram per hour, but a man, for example, needs only 2 to 3 times the volume of oxygen per kilogram per hour required by a bony fish. The problems faced by a mammal and a fish in obtaining these comparable volumes of oxygen are entirely different and, as will be seen later, the performance of the fish is perhaps the more notable.

(b) A COMPARISON BETWEEN AIR AND WATER AS RESPIRATORY MEDIA

Some of the differences in physical properties of air and water, from the respiratory point of view, are tabulated in Table 2. It is immediately apparent that the volume of oxygen contained in unit volume of air is very much greater than the maximum possible for natural waters. Consequently, to obtain 1cc of oxygen a fish must pass a far greater volume of the medium across its respiratory surface than a terrestrial vertebrate. Another aspect of this difference is that a litre of air contains sufficient oxygen to support a given animal about 25 times longer than a litre of water saturated with air. Moreover, water is far denser than air at the same temperature and its viscosity is much greater. There is also a very marked difference in the diffusion rates for oxygen and ventilation of the respiratory surface is therefore very necessary. This applies both to aquatic and terrestrial forms because even in a lung there is a thin film of

TABLE 2
Conditions for respiration in water and air

	<i>WATER (fish)</i>	<i>AIR (mammal)</i>
Respiratory organ	Gill – secondary lamella	Lung – alveolus
Respiratory current	Unidirectional and continuous	Tidal
O ₂ content of inspired medium	0.04–9.0 ccs/litre Tension = 1–200 mm Hg	105–130 ccs/litre. (Never 200 because of dead space) 80–100 mm Hg
% utilisation	up to 80 %	about 25 %
O ₂ diffusion rate	Low (CO ₂ , 23 × rate for O ₂ , at 20°C)	High ($\frac{1}{2}$ million × liquid)
Density	Specific Gravity of water about 1000 × Air (18° C)	
Viscosity	Water about 100 × Air	
CO ₂ content of expired medium	0–13 ccs/litre (often almost a 'CO ₂ vacuum') Tension = 0–10 mm Hg	110 ccs/litre 40–45 mm Hg
O ₂ consumption (resting)	50–100 ccs/kgm/hr (200 gm Carp)	200 ccs/kgm/hr (70 kgm Man)

water through which the oxygen must diffuse, but the distances are less than in aquatic forms. *Ventilation*, that is the pumping of the medium over the respiratory epithelium, requires the animal to do work, the amount of which is far greater in water than in air because of the higher density and greater viscosity. The liberation of energy for this work uses oxygen and in man it has been estimated that between 1 and 2 % of the oxygen uptake

at rest is utilised in the pumping of air in and out of the lungs. Accurate determinations of this figure have not been made for fish but there is little doubt that it will be greater than 10% and may be as much as 25%. Thus, if a trout increases its ventilation 4 times there is a 75% increase in oxygen consumption although there are no other apparent changes in its activity. When compared with terrestrial vertebrates, fish therefore seem to be at a distinct disadvantage from the respiratory point of view. One feature in which they do have advantages, however, is that the carbon dioxide can be removed from the respiratory system much more easily because of its greater solubility in water and the low concentration outside the fish.

Further complications arise for fish because of the effect of temperature on the oxygen content of the water and on the metabolism of the animal. These effects are most striking in fresh waters and the figures in Table 3 are for the oxygen con-

TABLE 3

Goldfish. The relationship between temperature, O_2 content of the water and the ventilation volume necessary to satisfy the resting metabolism. (Data of Fry and Hart, 1948)

<i>Temp. °C</i>	<i>Metabolism ccs O_2/kgm/hr</i>		<i>O_2 content of water ccs/litre</i>	<i>Ventilation Vol required litres/kgm/hr (75% utili- sation)</i>
	<i>Resting</i>	<i>Active</i>		
5	8	30	9.0	1.3
15	50	110	7.0	9.0
25	140	255	5.8	32
35	225	285	5.0	60

sumption of a goldfish at different temperatures when at rest, or swimming at constant speed. It can be seen that a seven-fold increase in temperature raises the resting metabolism 28 times but the oxygen available to the fish in unit volume of water

decreases very markedly. Consequently the volume of water necessary to supply sufficient oxygen to the fish increases about 46 times notwithstanding the assumption that it can extract 75% of the total volume of oxygen contained in the respiratory current. This high *utilisation* is a notable feature of the fish respiratory system but, even so, it cannot be maintained at very high volumes of pumping. Lowering of the utilisation aggravates the situation still further and it is easy to see that at a certain level all the extra oxygen that a fish is able to extract from the water will be used by the respiratory muscles themselves. Above this level the animal cannot possibly satisfy its oxygen requirements.

Although fish face many problems relating to their oxygen supply, and the gills may be the site of ionic exchanges, at least they are generally free from the dangers of desiccation which may be considerable on land. The thin film of moisture at the respiratory surface easily evaporates and may cause significant loss of water. This factor is important when the basic construction of these organs is considered. A very large surface is necessary but loss of water must be reduced. In terrestrial animals the increased surface results from the folding of an internal sac which communicates with the exterior through a relatively small opening. The cavity of this sac or *lung* can therefore remain almost saturated with water and loss through the respiratory opening is relatively slight. Aquatic forms do not have this problem because the respiratory surface usually develops externally as a much divided *gill*. Furthermore, this structure is well-supported by the aquatic medium and is not in danger of collapsing and the respiratory epithelium becoming occluded because of surface tension forces.

Despite the marked differences in the physical properties of air and water the fundamental processes of gaseous exchange at a gill and in an alveolus must be the same. This has been emphasized by the recent discovery that it is possible to maintain alive a mammal breathing liquid, provided that the partial pressure of oxygen in it is increased so that the diffusion gradient is adequate to meet the demands of the animal.

Aquatic Respiration of Fishes

The respiratory organs of fishes form the so-called 'gills'. These are diagnostic of all chordates and form a series of slits between the pharynx and the outside on both sides of the animal. In the earliest forms, a large number were present and they functioned not only for respiration but especially during feeding. This condition persists in primitive chordates such as *Amphioxus* and the sea squirts. During evolution the number of gill slits became reduced and most modern fishes have five pairs and never more than eight pairs. Even among terrestrial vertebrates a gill-slit stage is passed through in the embryo but the gills are not usually functional. The formation of the gills mainly involves activity of the endoderm which forms a series of pouches on both sides of the pharynx. These meet slight intuckings of the ectoderm and perforate to form gill slits, separated by the *gill bars*. It is the epithelium of these bars which becomes folded to form a series of filaments attached to the anterior and posterior face of each bar. Thus each gill or *holobranch* consists of two *hemibranchs* or sets of filaments attached to a gill bar and belonging to adjacent sides of two consecutive gill pouches. The gill bars are supported by the skeleton of the branchial arches.

The formation of gill slits is usually in step with the muscular segmentation but not invariably, for example in the Ammonoete larva of the lamprey. There seems little doubt that the two are segmented independently and that during phylogeny they have become intimately associated with one another.

In addition to these true gills, more superficial *external gills* are present during the development of fishes and Amphibia. Some of these, as in the early stages of all Elasmobranchs and

some teleost larvae (e.g., *Gymnarchus*), are prolongations of the gill filaments of the posterior hemibranchs. Their function in nutrition is probably as important as in respiration. The external gills of the free-living larvae of lungfish, *Polypterus* (a primitive bony fish), and Amphibia develop as outgrowths from the outer dorsal surface of the gill bars. They are therefore ectodermal in origin.

(a) RESPIRATION IN CYCLOSTOMES

One diagnostic character of lampreys and hagfishes is the presence of a relatively large number of gill slits. In the larval lampreys (Ammocoete) the respiratory current is produced by a velum which is also important in feeding. Food is trapped on the slits as in *Amphioxus* by means of mucus secreted by an endostyle.* These slits communicate between the pharyngeal cavity and the outside, but in adult lampreys the internal openings are to a separate diverticulum of the oesophagus. In the hagfishes, *Myxine* and the *Bdellostoma*, the gills open directly into the pharynx. The slits open separately to the outside in lampreys but in *Myxine* the external openings have coalesced so that only a single opening is visible on the outside of the animal. In addition on the left side there is a duct which connects the oesophagus with the exterior. This oesophageo-cutaneous duct is homologous with a gill slit but any gill lamellae are absent. In other hagfishes (e.g. *Paramyxine*) the coalescence of the external gill openings is less complete and in forms like *Bdellostoma* the gill pouches open separately to the outside just as in lampreys. The gill structure of both living and fossil cyclostomes is of the same general type, usually termed *marsipibranchs* or pouched gills. The pouches are inside the branchial skeleton which forms a complicated elastic network. The internal position of the respiratory epithelium relative to the visceral arch skeleton distinguishes them from the gills of true fishes, as does their blood supply. Each afferent vessel supplies the whole of a pouch, i.e. both the anterior and posterior hemibranch (fig. 1b).

* Midventral groove of the pharynx.

Fig. 1.

Myxine. (a) Longitudinal section to show the position of the velar chamber and the direction of the respiratory current when the animal is not attached to its prey. The distance between the velar chamber and the gill exits has been shortened as indicated by the dotted lines. (b) Pouched gill to show the direction of water flow opposite to that of the blood. Sphincters are present on the gill ducts at three points, (1) shortly after leaving the oesophagus, (2) before entering the gill pouch, (3) immediately after leaving the pouch. (Based on Cole, F. J. : *Trans. R. S. Edinb.* Vol. 49, 1913.)

The mechanisms ventilating the gill lamellae contained within the pouches are different in the two groups. Lampreys appear to remain attached to their prey for longer periods than do hag-fishes which have more of a scavenging existence, and their ventilation mechanism is well adapted to this situation. As the mouth is fixed to the prey by a suction mechanism, water cannot enter this way and consequently in lampreys the respiratory current passes through the external gill openings during both phases of the respiratory cycle. Expiration is an active process which results in constriction of the branchial region and the ejection of water from the individual pouches. The elastic recoil (fig. 4a) of the visceral arch skeleton produces a reduced pressure within the pouches which rises again as water enters them. The path of the water in and out of the external openings is not exactly the same, for they are guarded by valves which ensure that water passes through the gill lamellae only during the expiratory phase.

Recent work suggests that ventilation in myxinoids is completely different from that in lampreys despite the accounts given in many standard text-books. The mechanism appears to be the same both in free-living stages when the animal burrows in mud and during the relatively brief (four- to five-minute) periods when the animal 'burrows' into its prey. Water is drawn in through the nostrils and passes out through the external gill openings. The propulsion of this current is due to the *velum* contained in a special anterior chamber of the alimentary canal (fig. 1a). X-ray ciné films with contrast media in the respiratory chambers have confirmed this function, and have also revealed that parts of the respiratory tract may contract and assist the ventilation. There are also sphincters in the gill ducts on both sides of the pouches. It appears that these aid in the directional propulsion of the current but are also important as filters to prevent smothering of the gills. The frequency of the respiratory movements of *Myxine* is about 11–15 per minute.

In addition to the gill surfaces, a great part of the gaseous exchange of cyclostomes occurs through the skin and this is probably sufficient to satisfy the needs of *Myxine* during feeding.

Fig. 1. b.

Fig. 2.

The gills of teleost fishes. (a) View from left side to show the position of four gill arches beneath the operculum. (b) Filaments and associated structures attached to two neighbouring branchial arches. (c) Section through a secondary lamella, based upon electron micrographs. (a and b modified after Bijtel, J. H.: *Arch. néerl. Zool.*, Vol. 8, 1949).

The function of the oesophageo-cutaneous duct seems to be for the clearance of relatively large particles from the pharyngeal cavity. In addition, clearing the respiratory chambers of even larger particles can take place through the nostrils in a form of 'sneezing'.

(b) BONY FISHES

(i) *Gill structure*

Although the gill system of cartilaginous fishes probably represents a more primitive arrangement, from the functional point of view it is better to consider a bony fish first of all and then to discuss the differences shown by dogfish and sharks. Teleosts have four branchial arches (fig. 2a) on each side of the body which extend from the otic region of the neurocranium and join ventrally near the basihyal. Each of these arches has along its length a series of plates (the *filaments*) which form a double row splayed out as a V from the branchial arch skeleton (fig. 2b), and each filament is supported by a gill ray. The filaments are stacked one above the other and water passes in the spaces which lie between the filaments attached to each side of an arch. These spaces are not simple, however, for the upper and lower surfaces of each filament are folded into a large number of secondary folds or *secondary lamellae*. These folds are extremely thin for they are the site of the gaseous exchange, and water passes on both sides of them. A section across an individual secondary fold (fig. 2c) shows that it is made up of two very thin epithelial layers separated by a series of peculiar cells called *pillar* (or *pilaster*) cells and supported by a basement membrane. In life the gill filaments form a beautiful series of a delicate pink colour because they are very profusely supplied with blood. This supply comes from the ventral aorta and up each of the branchial arches there passes an afferent branchial artery. From these arteries a branch leads to each of the many filaments and in each filament the small afferent blood vessel divides repeatedly to supply each of the secondary lamellae. In the secondary lamellae

blood circulates through spaces formed between the individual pillar cells. It is a notable adaptation that the spaces between the pillar cells are just large enough for the red blood corpuscles to pass (fig. 2c). The distance for diffusion of O_2 between the water and corpuscles is small and can take place on both sides of the secondary folds. Having been oxygenated the blood is collected into a corresponding series of efferent vessels which pass into the efferent branchial artery which joins the dorsal aorta along which the blood passes back to the rest of the body.

(ii) *Counter-current principle*

The gills of fishes and many other aquatic animals show this principle extremely well; the essential feature being that the flow of water is in a direction opposite to that of the blood (fig. 3a). This pattern ensures that blood which has already become partly loaded with oxygen meets water which has had little O_2 removed from it. Correspondingly, water which has already had much of its oxygen removed is in contact with blood that is least saturated with oxygen. Therefore, a fairly constant gradient of oxygen tension between the blood and water is maintained throughout their passage across the gill. In this way a greater degree of saturation of the blood can be achieved and it is theoretically possible for the blood to reach almost the same oxygen tension as the inhalant water. In exchange systems with parallel flow, the gradient is initially high but will progressively decrease (fig. 3c and d). The advantages of counter-flow in heat exchangers are well known to engineers and, as we shall see (p. 88), they are similarly employed in vertebrate animals where efficient heat exchange is required. However, counter-flow is not always more effective than parallel flow. For instance, if water saturated with oxygen flows very rapidly past a respiratory surface in which a smaller volume of blood is circulating in parallel and at a much slower speed, the degree of oxygenation of the blood would be very nearly as great as if counter-flow were present. In this case the proportion of oxygen removed from the water would be relatively low whereas in fact bony fishes can achieve 80%

Fig. 3.

(a) Diagram to illustrate the counter-flow across a gill filament. (b) Profile of the sieve provided by secondary lamellae of three adjacent filaments. The water passes at right angles to the plane of the paper. (c) and (d) Theoretical graphs of the change in percentage saturation of the water and blood with oxygen during their passage across a secondary lamella. It is assumed that both fluids move at the same speed and have equal O_2 capacities. The flow is *counter* in (c) but *parallel* in (d). (a and b after Hughes, 1961.)

utilisation of the oxygen. When the direction of water flow is experimentally reversed in a tench the utilisation falls below 10%.

(iii) The water flow across the gills

So far we have assumed that all the water flows between the

secondary folds, but many diagrams of fish respiration suggest that a large volume of water can pass through the gaps or gill slits which are shown between the tips of the filaments attached to adjacent arches. However, these diagrams are based upon dead specimens in which the structure has become significantly modified from its condition in life. There are small adductor muscles (fig. 2b) in the septa of the gills which contract during fixation and draw the filaments of each branchial arch closer to one another and enlarge the slits. In life, however, the filaments are splayed out by the elasticity of the gill rays and the tips of the filaments attached to adjacent arches are in close contact with one another. This was first observed through a celluloid window in the operculum. The path of the water current across the gills, then, is mostly between the individual secondary folds of adjacent filaments which form a fine sieve similar in profile to fig. 3b. The dimensions show that the individual pores are very small but their number is so large that the total resistance to flow can be overcome without too much work. Such a sieve ensures that each part of the respiratory current is brought into intimate contact with a portion of the respiratory surface and diffusion distances within the water itself are kept to a minimum. The number of pores may be a quarter of a million in an average sized (150 grams) tench or trout and the total respiratory surface is up to ten times the total external surface of the animal. Also because of the very large number of pores, the water velocity past the secondary lamellae is not very great and the time for gaseous exchange is lengthened.

(iv) *Ventilation of the Gills*

The respiratory current of most modern fishes is produced by muscular activities which pump the water through the resistance provided by the gills. A common view that this ventilation mechanism is essentially a single pump is illustrated diagrammatically in fig. 4b. In this mechanism the whole of the buccal and opercular cavities would expand, drawing water through the mouth, and would then bathe the gills. Next the mouth would

Fig. 4.

Diagram of models to illustrate the mechanisms of ventilation in fishes. (a) Lamprey when attached to its prey, inspiration being due to the elastic recoil (spring) of the branchial skeleton. (b) Mechanism in teleost fishes if a single pump. (c) The double pumping mechanism which operates in bony and cartilaginous fishes. Water passes across the gills in three phases. In phase 4 there may be some reversal in the flow but this is a very brief part of the cycle. (c after Hughes, 1961.)

close and the almost simultaneous contraction of both cavities would force water out of the opercular openings. Flow of water

into and out of the system and across the respiratory epithelium would be intermittent.

The division of the respiratory chambers by gill resistances was not envisaged in this mechanism so that the hydrostatic

Fig. 5.

Movements of the mouth and operculum together with the pressure changes recorded in the buccal and opercular cavities of a trout. The dashed lines refer to the buccal pump and the continuous lines to the opercular pump. The differential pressure shows the greater pressure in the buccal cavity throughout most of the cycle and is striped during the phase when the water flow is produced mainly by the opercular suction pump. (After Hughes, G. M. and Shelton, G.: *J. exp. Biol.* Vol. 35, 1958).

pressure recorded in the buccal and opercular cavities would be almost identical throughout the whole cycle. In fact there are marked differences between them (fig. 5). It is now known that the mechanism involved is best considered as a double pump

(fig. 4c). The operation of the two pumps ensures that the flow across the gills is almost continuous despite its intermittent entry and exit from the system. Evidence for this view has been obtained by measuring the pressure changes in front of and behind the gills. The pressure curves (fig. 5) show that a gradient from the buccal to the opercular cavities is maintained throughout the respiratory cycle, with the exception of a very brief period when some reversal of flow may occur. This is unlikely, however, because of its extreme brevity and the inertia of the water. The buccal *pressure pump* forces water across the gills whereas the opercular *suction pumps* draw the water through them and the alternation and interaction of these two pumps maintains a continuous flow. An essential part of the mechanism is the presence of valves guarding the mouth and the opercular openings. Both sets of valves are passive and move according to the pressure gradient across them. Thus when the mouth opens, thin flaps of skin projecting down from behind the upper and lower jaws are displaced inwards by the reduced pressure. As the buccal cavity begins to decrease in volume the increase in pressure causes them to flap outwards, thereby closing the mouth and preventing too great a reflux of water through it. The rims of the opercula are also provided with a thin sheet of tissue which comes into close contact with the posterior border of the opercular cavities as they expand and prevents the entry of water by this route.

The operation of a double-pumping mechanism and the consequent continuous flow across the gills make the terms inspiration and expiration not entirely suitable. These are applicable to tidal ventilation but for fish a subdivision of each respiratory cycle into four parts is preferable (fig. 4c). The two main phases are when first the pressure pump and then the suction pumps are responsible for maintaining the flow. These two are separated by transition phases in which the differential pressure is reduced and may be reversed following the pressure pump.

(v) *Action of the skeletal and muscular systems during ventilation*

The skeleton of the teleost head is complex and varies from

species to species: the following account is based mainly upon the cod.* The functional relationships of the skeleton and muscles are illustrated diagrammatically in fig. 6.

As has been pointed out, the distinction between expiration and inspiration is not clear in fish because instead of tidal ventilation the water flows continuously across the respiratory epithelium. It is most convenient therefore to describe the functional system in terms of the muscles which alter the volume of the buccal and opercular cavities. Expansion of the buccal cavity

Fig. 6.

Diagram to show the position of the main muscles involved in respiration of an idealised teleost fish. The arrows point away from the insertion which normally moves. Dotted muscles lie beneath the skeleton. Muscles are numbered as follows: 1¹⁻⁴ adductor mandibulae (four parts); 3 levator arcus palatini; 5^{1,2} dilator operculi; 6, levator operculi; 7 adductor hyomandibulae; 7¹, adductor arcus palatini; 8 adductor operculi; 9, hyohyoideus dorsalis; 10, hyohyoideus ventralis; 11, protractor hyoidei (geniohyoideus); 31-34, adductors of branchial arches. 37, sternohyoideus.

Pmx, premaxilla; Mx, maxilla; LJ, lower jaw; Hmd, hyomandibular; Op, opercular; R, branchiostegal rays; Cl, cleithrum; Mx-Md Lig, maxillo-mandibular ligament. (After Hughes and Shelton, 1962.)

* For a detailed description of the skeleton and muscles, see Saunders and Manton, *Practical Vertebrate Morphology*, 3rd Edition. Oxford University Press, 1959.

takes place mainly in a ventral direction following contraction of the large sternohyoideus muscle which joins the pectoral girdle and basihyal. Lateral expansion of the buccal cavity is effected by contraction of a muscle with its origin on the otic capsule and insertion on the outer surface of the hyomanibula. This muscle is sometimes named the *levator hyoidei* but it is also frequently termed the *levator arcus palatini*. This also starts expansion of the opercular cavity; further abduction of the operculum is produced by contraction of the dilator operculi muscles. The opercular cavity also expands ventrally and laterally by the separation of the branchiostegal rays. This movement is produced by one of the hyohyoideus muscles. The relative size of the branchiostegal apparatus varies in different fishes, being highly developed in forms with well-developed suction pumps.

The decrease in volume of the buccal cavity begins with the relaxation of those muscles concerned in expansion, together with activity of the adductor mandibulae. This muscle is frequently divided into four parts, as in the cod, and it is mainly due to the action of parts 2 and 4 that the mandible is closed. Raising of the hyoid arch in the floor of the buccal cavity also plays an important part in the buccal pressure pump. This movement is achieved by contraction of the geniohyoideus (between the basihyal and mandible) when the adductor mandibulae is also contracted. Outward expansion of the buccal cavity is antagonised by the action of adductor muscles (adductor arcus palatini* and adductor hyomandibulae). The opercular cavity is decreased in volume by contraction of the adductor operculi and another part of the hyohyoideus muscle. The adductor operculi has its origin in a hollow of the otic region and is inserted on the inner side of the operculum. It functions by a lever system of the third order, which contrasts with the first order lever whereby the opercular cavity increases in volume when the dilator muscle contracts. The latter is inserted on the operculum dorsal and anterior to its articulation with the hyomandibula which forms the fulcrum.

* *Levator arcus palatini* of Saunders & Manton

This whole system is extremely complex and although the above account gives an interpretation of how the various movements can be brought about, it is by no means certain that such a description is accurate. It is possible, by recording the electrical activity in the respiratory muscles, to deduce more accurately the timing of the muscle contraction. From studies of this type it has been shown for example that the protractor hyoidei is active when the buccal cavity decreases in volume rather than when it is increasing. They have also emphasised the importance of couplings between the two pumps.

(c) CARTILAGINOUS FISHES

Ventilation in sharks and rays is also achieved by the operation of a pressure pump in front of the gills and suction pumps behind them. The pressure pump involves changes in volume of the cavity (*oro-branchial*) of the mouth and pharynx which extends into each of the gill pouches. There are usually five pairs of suction pumps each formed by the space (*parabranchial*) outside the gill filaments which communicates with the exterior through a gill slit. The slits are covered externally by flap valves formed by projections of the gill septum of the branchial arch anterior to the slit. It is the greater development of these septa which produces the more elongated branchial region of the dogfish, for example.

Another difference in selachian fishes is the persistence of the *spiracle*. Water enters the oro-branchial cavity through this opening as well as through the mouth. Fig. 7 shows how water entering by these two routes is distributed differentially through the gill slits. That entering the mouth leaves the three posterior slits whereas water entering the spiracle is mainly pumped out through the three anterior slits. Water is prevented from passing down the oesophagus by the contraction of a sphincter muscle, as in teleost fishes. Valves restricting the reflux of water from the mouth are present in many cartilaginous fishes although they are not so well developed in the common dogfish. The escape of water from the spiracle is prevented by the active closing of its opening by a valve which projects from its anterior border.

Water enters the oro-branchial cavity when its volume is increased by a lateral expansion and lowering of the floor, which mainly result from the elastic recoil of the head skeleton. The hypobranchial musculature only comes into action during hyperventilation and when the branchial region expands before biting. The valves of the gill slits are closed and water enters through the mouth and spiracle. During the subsequent decrease in volume produced by the action of the con-

Fig. 7.

Diagram of a dogfish in side view (anteriorly) and horizontal section (posteriorly) to show the path of the respiratory current. The flow is unilateral. The horizontal sections pass through the external gill slits and illustrate the changes in volume of the parabranchial and oro-branchial cavities. Pressures in these cavities are indicated with respect to zero pressure outside the fish. Full line arrows show the movements of the mouth and branchial regions, with their thickness indicating the relative strength of contraction.

strictor musculature, water is forced through the gill filaments and parabronchial cavities (fig. 7) before passing out of the gill slits. The actual path of the water current across the respiratory epithelium is difficult to determine, but by analogy with teleosts it probably passes between the secondary folds which project above and below the plane of each filament. This flow is once more opposite in direction to that of the blood but it is hindered by the well-developed inter-branchial septa.

The suction-pump mechanism is not so readily understood and is due to changes in volume of the separate parabronchial cavities. Pressure measurements show that the fall in pressure in these cavities is greater than that in the oro-branchial cavity during the expansion phase. Expansion of the parabronchial cavities is largely due to the elasticity of the branchial basket and especially of the gill rays which support the septa. The extent of this elasticity can be shown by compressing the branchial region of an anaesthetised dogfish. The gill pouches expand and the flap valves remain shut when the pressure is released and water is sucked in through the mouth. The parabronchial cavities are quite extensive, extending dorsal to their external openings, and the total capacity of the five pairs is fairly large. The volume of individual parabronchial cavities is decreased by contraction of the superficial constrictor muscles and water is ejected. During this phase the hydrostatic pressure in the oro-branchial cavity is greater than that in the parabronchial cavity and water is forced through the gill filaments. It is apparent therefore that as in the teleost fish a differential pressure gradient is present across the gills throughout the respiratory cycle. The flow of water is nearly continuous, which, together with the counter-current arrangement, helps to maintain a high utilisation of oxygen. Determinations suggest that the system is not as efficient as that of teleost fishes, for only about 50% is extracted.

(d) ECOLOGICAL VARIATIONS IN THE PATTERNS OF VENTILATION

Many fishes spend the greater part of their lives swimming in the open sea or fresh waters and only frequently come to rest on

the bottom. Some of these fishes do not make active respiratory movements when swimming, but rely upon the current entering the mouth as a result of their forward movement. This mechanism is found in some sharks but the best-known example is the mackerel which is unable to maintain full oxygenation of its blood when prevented from active swimming in an aquarium. In these instances, then, the passage of water across the gills is mainly due to a greater pressure in the mouth and is analogous to the pressure-pump mechanism. Indeed, pelagic fish which do not rely on the current resulting from their swimming movements depend on the buccal pressure pump far more than the suction pumps for ventilation of the gills. At the other extreme fish which spend most or the whole of their lives on the sea bottom depend to a far greater extent on suction-pump mechanisms (fig. 8). Such teleosts as the dragonet, plaice, sole, and other flatfishes are notable teleost examples and rays and skates among the cartilaginous fishes also show greater dependence on their parabranial suction pumps. Further adaptations of these bottom-living forms are found in the position and nature of the opercular openings. In the gurnard, for example, the exit of water from the opercular cavities is restricted to a small dorsal portion of the total opercular opening (fig. 8). The dragonet shows a similar dorsally-directed respiratory current and in this case the opercular cavity only communicates with the exterior through a small hole. In flatfishes, both bony and cartilaginous, it appears that the opercular and gill-slit openings may be actively closed and so prevent the entry of any sand grains into the gill chambers. Fish which lie on one side, such as plaice, use the gills on both sides which are equally developed as are the opercula.

Most cartilaginous fishes are heavier than water and when at rest they sink to the bottom. The presence of the dorsally-directed spiracle may be associated with this feature for it enables clean water to be respired when the fish is on the bottom. There is a rough correlation between size of the spiracle and habit of the fish. It is absent in the pelagic *Holocephali* (which also have an operculum) and is relatively small in pelagic sharks but is extremely well developed in the bottom-living skates and rays. In

Fig. 8.

(a) Differential pressures recorded from several teleost fishes to show the importance of the suction pump (shaded) in bottom-living forms. The numbering corresponds to the four phases of Fig. 4c. Note the absence of any reversal in the plaice. (After Hughes, G. M., *J. exp. Biol.* Vol. 37, 1960.) (b) The ejection of the respiratory current dorsally from the opercular cavities is illustrated for the gurnard and dragonet.

the latter fish most of the respiratory current enters the spiracles, whose valves are well developed, and as they operate rhythmically produce the characteristic 'winking' movements of these fish.

In fishes which only spend part of their time on the bottom, intermediate stages are found in the relative development of the pressure and suction pumps. In the bony fishes these forms also show an intermediate condition in the development of the branchiostegal rays which form an important part of the highly developed suction pumps of benthic forms.

Most fishes have mechanisms for cleaning and protecting the gill epithelia. In some teleosts, for example the carp family, the presence of regular 'coughing movements' is well known. During these movements the respiratory current is reversed to a greater or lesser extent and under certain conditions the movements may be very forceful. Among cartilaginous fishes reversal of flow from the parabronchial cavities results in water being forced out through the spiracles. It is a common sight when skates and rays are flapping about on the deck of a trawler to see water spouting out of their dorsally-situated spiracles. These 'spouting' movements form a regular part of the breathing rhythm in these fishes, although their frequency is less when the water they are inspiring contains little suspended matter. During these movements producing reversal of flow the external openings of the gill slits or the opercular openings are actively closed. In teleost fishes contraction of the adductor muscles draws the filaments attached to each branchial arch closer to

Fig. 9.

Graphs to show the way in which the ventilation or minute volume of a tench is increased partly by the frequency (crosses) and partly by an increase in stroke volume. (Hughes and Shelton, unpublished.)

one another. The size of the gill slits is increased and hence the resistance to the reversed flow diminishes. In elasmobranchs each branchial arch only has a single row of gill rays and it is doubtful whether similar mechanisms are found.

Further differences between fishes are found in the way they vary the volume of water pumped across the respiratory epithelium. Obviously this may be achieved by changing either the frequency of the respiratory rhythm or the volume of water pumped for each respiratory cycle (stroke volume). Relatively few fishes have been investigated from this point of view. A trout of 900 grams pumped 8 litres of water per hour at 10–12° C when at rest. During more active ventilation, because of more CO₂ or less O₂ in the water, the respiratory volume may be increased to 40 litres per hour. This increase is accomplished mainly by a greater stroke volume, for the frequency remains about 60 per minute at all ventilation volumes. In the eel, however, any increase in ventilation volume is achieved by a combination of both stroke volume and an increase in frequency, whereas in a tench it is achieved mainly by increasing the stroke volume (fig. 9).

Air-breathing in Fishes

Because of the greater volume of oxygen in unit volume, it might be expected that the conditions for the respiration of all animals would be more favourable in air than in water. This is not true for fish, however, because their very fine adaptations to an aquatic existence make it difficult for them to take advantage of the more favourable O_2 supply. Most fish die out of water because the gills collapse under the forces of gravity and surface tension which bring the secondary lamellae together as the water between them is lost and consequently the effective respiratory surface is reduced. There are some fish in which special supporting tissue is present which decreases the rate of water loss and restricts such a collapse e.g., some gobies, including the mud-skipper (*Periophthalmus*), which live on shores where they are liable to find themselves out of water. Other fish, notably eels, make migrations across land through moist grass and under these conditions they rely almost entirely on gaseous exchange through their skins. *Cutaneous* respiration is also used by these fish when in water as well as by a number of other aquatic vertebrates which usually have smooth and slimy skins.

When an ordinary marine or fresh-water bony fish (in addition to mud-skippers etc.) is taken out of water, similar physiological changes are found to those which occur when a mammal dives (pp. 62–63). For instance the heart beat of a carp slows from 60/minute to 5/minute and frequently the respiratory movements are inhibited. Another similarity is that a great deal of lactic acid enters the blood when the fish is returned to its normal environment. This suggests that when it is out of water anaerobic respiration proceeds in the tissues but its products are prevented from circulating to other parts of the animal.

(a) ACCESSORY RESPIRATORY ORGANS

There are, however, quite a number of fish which are able to breathe air and habitually do so because of the low O_2 content of the water which they inhabit. These are usually found in swamps; those of Paraguay and East Africa have been most studied, where the concentration of oxygen in the water ranges from 4.5–5.0 ccs per litre in the creeks, down to 0.2–2.0 ccs in the swamps themselves. These low oxygen concentrations are due to the stagnant conditions which allow the accumulation of decayed products and in many cases the poor light which reduces photosynthesis of any aquatic plants. Furthermore, the temperature of these waters is high and so is the CO_2 content; by no means ideal conditions for aquatic life. Many different species of fish live in waters of this type, however, and it has been found that they obtain their oxygen in one of two ways. The first group obtains sufficient oxygen from the thin film at the surface which is in contact with the air and remains relatively well oxygenated. The majority of fish live in deeper waters and possess some sort of accessory breathing organs. These organs are found in many parts of the body, usually a highly vascularised portion of the alimentary canal that is covered with a thin respiratory epithelium where gaseous exchange takes place. The fish comes to the surface periodically to swallow air which passes to the appropriate part of the gut and oxygen is absorbed. The frequency of the visits to the surface increases at lower oxygen tensions. Such accessory organs are found in species from many different groups of fishes and there is little doubt that they have been independently evolved to meet the stringent requirements of these habitats. Many striking examples of convergent evolution are known. Correlated with the independent origin of these organs, we find associated differences in their blood supplies. They are usually supplied with blood from the same vessel that would supply them if they were parts of a normal alimentary canal (Table 4). Typically, for example, those which are modified portions of the stomach, intestine or rectum receive their blood from the coeliaco-mesenteric, or posterior mesenteric arteries,

and the venous return is collected into the hepatic portal vein before entering the liver. This efferent blood vessel, of course, will contain more highly oxygenated blood than that which comes to it from the dorsal aorta after its passage through the less well-developed gills. In conditions where the gills are able to oxygenate the blood sufficiently, the accessory organ is scarcely functional and at most acts as a booster station.

TABLE 4
Blood supply to accessory respiratory organs

<i>Fish</i>	<i>Position of accessory organ</i>	<i>Afferent Vessel</i>	<i>Efferent Vessel</i>
A. Efferent return same as normal circulation			
1. In <i>parallel</i> with the gills			
<i>Clarias</i> <i>Saccobranchus</i>	Epithelium of branchial cavity	Afferent Branchials	Efferent Branchials
2. In <i>series</i> with the gills			
<i>Electrophorus</i>	Pharyngeal epithelium	Aortic Arches	Jugular v. & Ant. Cardinal
<i>Anabas</i>	Sub-opercular cavity (Labyrinthine organ)	All efferent Branchials	Jugular v.
<i>Plecotomus</i>	Stomach	Coeliac	Hepatic Portal v.
<i>Polypterus</i> <i>Amia</i>	Lung Swimbladder	6th Arch 6th Arch	Hepatic v. Left Ductus Cuvieri
B. Efferent return direct to heart			
<i>Gymnarchus</i>	Swimbladder	5th & 6th Efferent Branchials	Direct vein to auricle
Dipnoi	Lung	6th Arch	Pulmonary Vein

(b) LUNGS AND THE SWIMBLADDER OF FISHES

One part of the alimentary canal from which accessory respiratory structures are frequently derived is of particular interest because of its relationship to the breathing organs of tetrapods. This is the pharynx from which diverticula form the lungs of the Dipnoi (lungfishes), the primitive bony fish, *Polyp-terus*, and the swimbladder of most teleost fishes. In some instances, e.g., *Erythrinus*, the swimbladder has secondarily acquired an accessory respiratory function.

The distinction between lungs and swimbladders is usually based upon their ventral or dorsal origin from the pharynx. As in tetrapods, lungs have a ventral origin although they may come to lie dorsal to the alimentary canal. Swimbladders always lie dorsal to the alimentary canal and may or may not retain their connection with the pharynx via the pneumatic duct. No definite evidence is available for deciding which of these structures is the more primitive, although some very early fish (e.g., the Silurian Placoderm *Bothriolepis*) appear to have had ventral pharyngeal diverticula. Comparative anatomy supports the view that a bilobed lung was the most primitive condition. On the line of evolution which gave rise to tetrapods this structure persisted and is homologous with the tetrapod lung. The lungfishes diverged from this line quite early, but the lung persisted and enabled them to inhabit swamps liable to drying up. It is probable that both of these lines of evolution took place in fresh waters, but the other main line of bony fish evolution resulted in the invasion of marine waters. Here the dangers of periodic drying up were negligible and in association with this the air-breathing function of the lung became lost. Correspondingly, greater adaptation to a pelagic mode of life occurred and the pharyngeal diverticula became hydrostatic in function. As this is one of the most fascinating modifications of a respiratory organ in vertebrates it will be considered in detail before discussing the breathing of lungfish and its relationship to the evolution of the double circulation.

(c) THE SWIMBLADDER

In general, the swimbladder is found in all teleost fishes, though it is without trace in the cartilaginous fishes. There are some notable exceptions among bony fishes which are not unexpected in the light of its normal function. It is not found, for instance, in fish which spend most of their time on the sea bottom and rarely rise above its surface. These include many inshore fishes such as gobies, bullheads and the dragonet. Plaice, sole, flounders and other flatfishes also have no swimbladder. Another group in which it is absent are fishes living in turbulent rivers and mountain streams, but perhaps the most surprising group are fast ocean-swimming fish such as the mackerel and some tunny. In these forms, which keep swimming to maintain their respiratory current, it has been calculated that the absence of a swimbladder decreases the muscular effort required during swimming as well as removing any limitation on their vertical migration.

(i) *Structure of the Swimbladder*

The structure of the swimbladder is fairly uniform and the basic layers of the alimentary canal can be recognised. Two layers, tunica externa and tunica interna, are usually distinguished. The outer layer is often highly extensible and consists of a trellis of elastic fibres. The tunica interna has no elastic fibres but contains collagen and smooth muscle. Other features of the blood supply and structure of the swimbladder are shown in fig. 10. In most swimbladders, two distinct vascularized regions are recognised, one of which is ventral and called the *gas gland*. Dorsally and posteriorly is found the *oval*, so called because of its shape when viewed from inside the bladder. It is now established that the gas gland is concerned with secretion of the swimbladder gas and the oval with its re-absorption into the blood stream. During secretion the absorptive epithelium of the oval is removed from contact with the contained gas by the contraction of a sphincter muscle (fig. 10a).

Secretion of gas into the bladder is a complex and incom-

Fig. 10.

Diagrams to show the structure of a physoclistous swimbladder. (a) General organisation and blood supply. (b) Transverse section through the rete mirabile to show the close relationship between afferent and efferent capillaries. (c) Diagram illustrating the role of the hair-pin counter-current in maintaining the very large difference in O₂ tension between the contents of the bladder and the blood supply in a deep-sea fish. The arrows indicate the diffusion of oxygen across the rete. (b and c after Scholander, 1958.)

pletely understood process. It is associated, however, with a remarkable structure of the capillaries in the gas gland. The afferent vessel divides into a large number of parallel running branches which come near to the surface of the secretory epithelium and then double back on themselves in a sort of hair-pin bend and on their return become very closely apposed to the afferent capillaries. A cross section (fig. 10b) of this whole structure, the *rete mirabile*, gives the impression of a draughts board, the black and white squares of which represent the afferent and efferent vessels respectively. It is evident that such a structure will greatly facilitate the exchange of gases between

the two sets of vessels and that this will be further aided by the counter-current. It is believed that in this way a considerable difference of oxygen tension can be maintained between the efferent blood and the swimbladder gas (fig. 10c). Thus, oxygen secreted into the swimbladder so as to maintain hydrostatic equilibrium in a fish which swims to a greater depth does not get lost via the circulation. For, although the blood may reach equilibrium at the higher partial pressure of oxygen in the swimbladder gas, during its passage away from the bladder this blood will be close to blood of lower oxygen tension and the extra oxygen will diffuse across the thin membranes of the rete mirabile. In this way the counter-flow will ensure that there is scarcely any loss of oxygen from the bladder.

The gas secreted into the swimbladder is mainly oxygen but there is also present some nitrogen and rare air gases such as argon. All the oxygen comes from the molecular oxygen contained in the water, which at depths of two to three thousand metres remains at the same tension as the surface, i.e., one-fifth of an atmosphere. Swimbladders of fishes at these depths may contain 90% nitrogen, and if constant volume is maintained the oxygen in the bladder must be at a partial pressure of two to three hundred atmospheres. It is evident, therefore, that the blood in the hairpins of the rete mirabile must be in equilibrium with this gas although when it passed through the gills it was in equilibrium with the tension of oxygen in the water. The performance of the rete in preventing the loss of oxygen at these very high pressure gradients is quite fantastic, for the tension must drop nearly 3,000 times during its passage along 1 cm. of capillary. In terms of heat in a counter-current exchange system it is as though boiling water passing in at one end and ice-water at the opposite end were in contact for only 1 cm. yet the heat transfer was complete to within 1 ten-thousandth of a degree!

(ii) *Functions of the Swimbladder*

The swimbladder wall is supplied with sensory endings which probably detect the degree of stretch of the bladder wall produced by changes in volume of the bladder. This may result from

changes in depth of the fish or the effect of sound vibrations in the water. The detection of sounds, however, is best done by those fishes which have some connection between the swim-bladder and the inner ear. For example, cyprinoid fishes such as carp, tench and minnow possess *Weberian ossicles* which transmit vibrations of the anterior sac to a part of the inner ear. Conditioning experiments have shown that these fish are able to respond to higher frequencies (e.g., 10,000 c.p.s.) than most other fish which do not possess them. This apparatus also serves to detect slow changes in volume of the more extensible anterior sac resulting from slow changes of ambient pressure such as the fish will experience if its depth below the surface changes. In other fishes the swimbladder is concerned in the production of sounds, usually by the operation of special muscles attached to the swimbladder, but in other cases it functions as a resonator to amplify such sounds.

The most important and primary function of the swim-bladder, however, is to regulate the density of the fish relative to the surrounding medium. Evidence strongly suggesting such regulation is fairly clear when a bony fish is observed freely floating in an aquarium tank, for it maintains its position neither moving up or down in a state of neutral buoyancy without making any active movements. A second piece of evidence comes from measurements showing that the density of fish tissues is about 1.076. In fresh water a fish of this density would sink to the bottom, but by containing a bubble of gas the density of the whole fish is reduced to that of the external medium. It can be calculated that the volume of such a bubble must be about 7 ml. for a 100-gm. fish in freshwater and 5 ml. for a marine fish. Determinations of the volume of swimbladders (Table 5) of many bony fishes have confirmed that this size of bladder is generally found.

The presence of such a bubble of air in an organism means that it will be affected when the hydrostatic pressure surrounding it is altered. Increasing the pressure will decrease the volume of gas and consequently the density of the whole fish will be reduced. Conversely, reductions in pressure will cause the swim-

TABLE 5
Size of the swimbladder of teleost fishes

	<i>% volume of swimbladder</i>	<i>Highest frequencies to which responds (c.p.s.)</i>
Catfish	5.8	13,000
Goldfish	7.9	3,000-4,000
Dace	9.0	
Eel	3.7	500-650
Goby	1.2	600-800
Wrasse	4.9	
John Dory	4.3	
Mackerel	Absent	
Dragonet	Absent

Fig. 11.

Diagrams of an experiment in which the pressure above a physostomatous fish is reduced and leads to the release of gas from the swimbladder, (a). Two such 'deflated' fish (Crucian carp) are placed in a tank and one only (b) is allowed to reach the surface and gulp air. This fish becomes neutrally buoyant again, but the other (c) sinks to the bottom when at rest.

bladder to increase in volume and the density of the fish + swimbladder will fall.

This latter condition is very easily demonstrated experimentally in a large flask as shown in fig. 11. The decrease in pressure tends to make the fish rise and elicits compensatory movements of the animal. In the case of *physostomatous* fishes (i.e. with the swimbladder still connected to the gut) the reaction is a 'gas-spitting reflex' whereby air is ejected from the bladder following relaxation of the pneumatic duct sphincter. The loss of gas reduces the density of the fish + swimbladder and it is thus restored to neutral buoyancy at the lower pressure. In *physoclistous* fishes (e.g. Perch) such a reaction is not possible because the swimbladder is isolated, and the animal makes compensatory movements of the pectoral fins which increase in frequency as the force tending to raise the fish increases. Further decreases in pressure result in active movements of the tail, at first asymmetric contractions of the lobes of the caudal fin and later strong downward swimming. Over long periods such fish depend entirely on their ability to reabsorb gas at the oval. When the pressure is restored to its original level the compensatory movements stop. In physostomes in which the volume of swimbladder gas has been decreased, the fish is more dense than water and it tends to sink to the bottom of the tank. It soon swims to the surface and attempts to replenish the gas lost from its swimbladder by gulping air. If this is prevented, however, the fish continues to strive for the surface but eventually neutral buoyancy is restored by gas secretion.

This experiment is equivalent to the situation which arises when a fish swims rapidly towards the surface of the ocean. Under such conditions the swimbladder will rapidly expand, the density of the fish is reduced and it will tend to rise even more rapidly to the surface because of its lowered density. This shows the basic instability which is intrinsic to this system of maintaining a buoyant condition. This factor effectively limits the rate at which fish can migrate vertically in the sea and those without a swimbladder are at a distinct advantage. It has been calculated that a fish at 20 m. depth may swim rapidly to about

15 m. but no higher; for its compensatory movements are insufficient to prevent it being taken up to the surface because of the expansion of its swimbladder. It may rise further, of course, but this must be done slowly because of the slow rate of the processes reducing the swimbladder volume. Studies of the vertical migration of fishes using echo-location have shown the presence of the so-called deep scattering layer which moves up and down in a diurnal rhythm. The cause of this layer is incompletely understood but many experts consider it to be due to the reflection of the waves by the swimbladder. The swimbladder is also important economically because when the catch of a trawler is raised very rapidly to the surface the gas contained in the swimbladders will expand and frequently it may burst and cause sufficient damage to the catch to render it a financial loss.

The absence of swimbladders in deep-water fishes is readily understood because they are subject to such enormous pressures that secretion would need to be very great and would have such a limiting effect upon their movements. Those which are habitually bottom-living do not require to be neutrally buoyant when at rest. The difficulties of vertical migration could be overcome if the swimbladder were made of steel and were prevented from changing in volume as the fish swam towards the surface. It is notable that some of the fishes of abyssal groups (e.g. Coelacanth) had ossified swimbladders. And in the cartilaginous fishes the problem is overcome by adjustments of the total density of the fish resulting from the presence in the liver of fats of very low specific gravity.

(d) RESPIRATION OF LUNGFISHES (DIPNOI)

Lungfishes arose in the Devonian period and have a long fossil history. They are closely related to the group of fishes (Crossopterygii) which gave rise to the first land vertebrates. In common with crossopterygian fishes they possess internal nostrils which can be seen in the three living genera of lungfishes. These are found in the three southern continents and are *Neoceratodus* (Australia), *Protopterus* (Africa), and *Lepidosiren* (South America). As their common name suggests, all three

genera have a diverticulum of the pharynx (bilobed in *Protopterus* and *Lepidosiren*), which can be used to breathe air. The order of the three genera given above is one of increasing ability to breathe air and a decreasing ability to survive aquatic conditions. Only *Neoceratodus* is able to survive if it is not allowed to come to the surface and only this genus has well-developed gill filaments. Also correlated with their different abilities with respect to aerial and aquatic respiration are differences in the circulation to the branchial region. The branchial arches of *Lepidosiren* pass through the gill arches with few capillaries and the blood does not come into close contact with water. In *Neoceratodus* the branchial arches break up into fine capillaries in the gills. It normally breathes under water with the mouth slightly open and a current produced by slow movements of the two opercula. This Australian lungfish rarely comes to the surface, but the other two genera regularly (e.g. every 15–30 minutes in *Protopterus*) come to the surface and gulp air through the mouth. Notwithstanding the presence of internal nostrils in the Dipnoi, it appears that air is always taken in at the mouth in those living fishes which breathe air. It might be supposed that air enters through the nostrils during periods of drought. In fact only *Protopterus* makes a mud cocoon although *Lepidosiren* is also able to aestivate, but *Neoceratodus* cannot survive out of water for long periods. In *Protopterus* there is a well-defined plug of mucus in the nostrils and the cocoon only communicates with the air through a tube which enters the mouth. In this case, then, there is again no doubt that air-breathing does not take place through the nostrils.

Living in a cocoon during periods of drought is a very good adaptation where such periods are lengthy and *Protopterus* may survive as long as 3–5 years in such a state. As long as the cocoon remains intact the fish is protected against desiccation. Its entry into aestivation is a well-defined response to conditions where the water level falls and the habitat becomes muddy. The fish dives into the ooze and turns upwards so that its snout lies just below the surface of the water. As the water level falls still further the fish makes occasional excursions to the surface and

this leads to the hollowing out of a chamber which opens to the air through a small blow-hole. Finally, the water drains away completely and the fish is able to breathe without coming to the surface. It curls up with its tail above the head and covering the eyes. Mucus covering the body dries into a hard cocoon which only opens to the outside through a funnel which extends into the mouth. The wall of the cocoon has lipo-protein waterproofing layers similar to those of the insect egg.

During aestivation the animal is unable to feed and there are some interesting adaptations in its metabolism. These have been investigated by keeping African lungfish in the laboratory without food for varying periods. During such fasting the oxygen consumption of the animal falls gradually to levels which are determined by the time since it last took food. Similarly within the cocoon the O_2 consumption falls by 50% during the first week and finally after several months to only 10% of its initial level. Correlated with the reduced metabolism *Protopterus* breathes only once every hour or two and its heart rate is only 3/minute. If the cocoon is carefully removed the fish is found to be moist inside and if kept in a suitable chamber for several days it may remain motionless, except for the infrequent respiratory gasps. Awakening from this remarkable state of dormancy is readily induced by the threat of asphyxiation. Unlike other fishes the entry of water to the mouth results in attempts to breathe air and finally convulsive jerks as it awakens. After awakening, there is a rapid increase in body weight before the animal feeds and this is due to the intake of water.

Respiration of Tetrapods

With few exceptions the respiratory organs of tetrapods are paired hollow sacs or lungs. They are absent in some Amphibia, notably salamanders living in torrential streams, and reduced in forms which have external gills as adults. The lungs develop as ventral outgrowths of the pharynx and although their precise phylogenetic relationships are not clear, it is generally accepted that they are homologous with the swimbladder and lungs of fishes. Their blood supply is derived from the sixth aortic arch of the embryo and oxygenated blood is returned directly to the heart in a pulmonary vein. All lungs have a thin epithelial layer abundantly supplied with blood but their internal complexity varies a great deal. In many amphibia it is little more than a hollow sac, as in lungfishes, there being few infoldings of the internal wall to produce an increase in surface area for gaseous exchange (fig. 12). In the common frog, however, the surface is extensively folded and externally it has a foamy appearance. The two lungs communicate separately with a single laryngo-tracheal chamber which is supported by small cartilages but there are no well-defined trachea or bronchial tubes. This chamber opens into the hind end of the pharyngeal cavity through a slit-like *glottis* which is operated by muscles. The respiratory surface of *Rana* corresponds to no more than 20 sq. cm. for each cc. of air contained within the lung. In comparison with the latter figure, a man's lung has 300 sq. cm. of alveolar surface for each cc. of air. The walls of the lungs contain numerous elastic fibres and plain muscle fibres are also present which enable the lung to make spontaneous contractions when isolated.

Fig. 12.

Diagrams of the lungs of tetrapods to show the increase in the infolding of their surfaces. (a) *Proteus*, (b) *Siren*, (c) *Rana*, (d) *Sphenodon*, (e) *Varanus* (a lizard), (f) *Thassochelys* (a turtle) (g) *Chamaeleo*.

(a) VENTILATION IN THE FROG

When a frog is observed at rest, movements of the throat are visible at frequencies between 80 and 120 per minute (fig. 14). These form the so-called *Bucco-pharyngeal* movements. During this activity the nostrils are partly open and the glottis closed with the result that air contained in the bucco-pharynx is constantly renewed. Gaseous exchange is thought to occur in the vascularised mucous membranes and would assist in respiration, but some authors have doubted whether its contribution is very significant. The movements are produced by contractions of the mylohyoideus muscle, which is a thin sheet of fibres running transversely between the two rami of the lower jaw.

Periodically these small fluctuations of the throat are interrupted by quite large gulping movements which coincide with movements of the flanks of the frog. The mechanism of this *pulmonary ventilation* is essentially a buccal force-pump, involving changes in volume of the buccal cavity co-ordinated with the operation of valves in the nostrils and the glottis. It may also be assisted in some forms by active movements of the flanks. The mechanism is illustrated diagrammatically in fig. 13 where four main phases are recognisable.

In the first stage (1), the glottis is closed and the nostrils open. The floor of the mouth is lowered by the action of the sternohyoideus muscle and air enters the bucco-pharynx because of the reduction in pressure. In the next stage (2) the nostrils are closed, the glottis is open and air is forced from the lungs into the bucco-pharynx as the flanks contract, partly because of the elasticity of the lungs. The effects result in a passive extra lowering of the floor of the mouth. The mixed air now contained in the bucco-pharyngeal cavity is forced into the lungs (3) through the open glottis; this is brought about by contraction of the petrohyoideus muscles which raise the hyoid plate. The latter activity may be repeated several times until finally (4), with the lung filled, the glottis closes and the extra air is forced out through the open nostrils.

Variations on this plan have been described for different

Fig. 13.

Diagrams to show four stages in the pulmonary ventilation of a frog. Full lines indicate 'fresh' air; dashed lines — used air. Thick arrows show the major movements, probably active, during each phase.

Fig. 14.

Rana. Recordings of the movements of the floor of the mouth and flanks during respiration. The regular bucco-pharyngeal movements are interrupted by periodic ventilation of the lungs. The four phases of fig. 13 are indicated in the faster recording of one such movement cycle.

species of frog but the essential mechanism is the same and involves co-ordinated activity of the nostril valves, glottis, and hyoid apparatus. After periods of intense activity, frogs may show continuous pulmonary ventilation but at rest it is more usual to observe bucco-pharyngeal movements interrupted periodically by the pulmonary movements (fig. 14.) Evidently these movements bring about renewal of the air in the bucco-pharyngeal cavity which is then pumped in and out of the lungs until a good proportion of its oxygen has been removed before its expulsion. In this way maximum use is made of the oxygen and water loss is kept to a minimum.

The mechanism of the nostril valves in frogs is different from that of most other Amphibia where they are controlled by sphincter muscles. When the mouth is closed firmly, pressure of the lower jaw between the premaxillae is transmitted to the nasal bones which move in such a way that the external nostrils are closed. This can be demonstrated quite easily in a live frog by opening the mouth and pressing with a seeker on the inside of the upper jaw just behind the premaxillae. The internal nostrils are also visible in the roof of the mouth as quite large and widely separated openings and it has been suggested that they are closed by the action of the anterior horns of the hyoid plate. The distance separating these horns is similar to that between the internal nostrils which they will occlude when the hyoid is raised. The whole of the external rim of the buccal cavity is firmly closed when the jaws are pressed together and it is evident that this cavity may become completely air-tight when air is forced into the lungs. The glottis is supported by cartilages and its slit-like aperture is controlled muscularly.

Many Amphibia are able to live beneath the surface for very long periods. For example, the clawed toad, *Xenopus*, can remain under water for two weeks or more and remain alive. Under these conditions, oxygen is mainly obtained through the skin which is profusely supplied with blood derived from the pulmo-cutaneous arch. There is no doubt that *cutaneous respiration* plays a very important role in several of the lower tetrapods, and in frogs it has been shown that the amount of

gaseous exchange at the skin varies at different times of the year. (Table 6). Most of the CO_2 loss is through the skin at all times of the year but the uptake of oxygen by this route is most important during the winter months. Cutaneous respiration accounts for two-thirds of the total oxygen uptake during the winter but only a quarter in the summer. The actual volume of

TABLE 6

Frog. Seasonal differences in gaseous exchange (after Krogh, 1941)

Date	Weight	Respiratory exchange (ccs/kgm/hr)					
		Cutaneous		Pulmonary		Total	
		O_2	CO_2	O_2	CO_2	O_2	CO_2
9 April	46g.	51	145	160	70	211	215
7 October	54g.	54	92	51	15	105	107

oxygen absorbed through the skin remains constant throughout the year, the change in proportion being due to a considerable increase in the oxygen entering via the lung and the carbon dioxide leaving by that route.

The surface area of the skin of a frog is much greater than that of the lung, being about 12.5 sq. cm./gram compared with 8.4 sq. cm./gram. for the lung surface. (The latter figure is high relative to other measurements on frogs, see Table 1.)

(b) RESPIRATION OF REPTILES

Reptiles are better adapted to a land habit than amphibians and this is associated with more efficient ventilation. The lungs have an increased internal surface and they communicate with the pharyngeal cavity by a distinct tracheal tube supported by circular rings of cartilage. Some of the less active forms, however, have simple bag-shaped lungs as, for instance, in *Sphenodon* (the Tuatara of New Zealand), but in larger lizards (e.g., *Varanus*) the surface is greatly increased and definite bronchial tubes may be recognised in the lung (fig. 12). The wall of the lung

is supported by elastic fibres and once again plain muscle fibres enable the lung to make spontaneous rhythmic contractions. In some forms, such as chamaeleons, the presence of extensions of the lung into air sacs is suggestive of a condition much elaborated in birds. The air sacs do not contain any respiratory epithelium and only appear to be important in ventilation. Many reptiles have secondarily acquired an aquatic habit which in some instances is associated with a decrease in the respiratory area (Table 7). In aquatic turtles, for example, the lung volume is about 3-6 ccs./100gm. whereas in their terrestrial relatives it may be 21 vols. %.

TABLE 7

Lung size of turtles from different habitats (after Agassiz, 1857)

<i>Species</i>	<i>Habitat</i>	<i>Body weight (Kgms.)</i>	<i>Lung capacity (ccs.)</i>
<i>Testudo polyphemus</i> (Gopher)	Dry ground and sand holes	2.69	574
<i>Chelydra serpentina</i> (Snapping turtle)	Water and mud	1.84	115
<i>Trionyx ferox</i> (Soft-shelled turtle)	Water and mud	2.14	74

As in amphibians, three mechanisms for obtaining oxygen have been described; bucco-pharyngeal, pulmonary, and cutaneous. The last of these is apparently not so important because the horny layers of the skin not only prevent water loss but also hinder any gaseous exchange. There is evidence for the importance of cutaneous respiration in some aquatic reptiles. Oscillations of the pharyngeal floor occur in many reptiles but their function is doubtful. Any gaseous exchange which they assist is very slight, as shown by determinations of the carbon dioxide content of the expired air; their function appears to be mainly olfactory. Pulmonary ventilation is of major importance,

the lungs being filled by the action of a *costal pump*. Ribs are absent in modern Amphibia although they were found in their mesozoic ancestors but they are universal among reptiles. Movement of the ribs is produced by the intercostal muscles which expand the cage in the thorax and produce a reduction of the pressure within the lung. Inspiration is therefore active and a suction pump is the main mechanism ventilating the lung. Expiratory movements are partly passive but may be assisted by contraction of transverse abdominal muscles and the smooth muscles of the lungs themselves.

More detailed studies of ventilation in lizards have led to the description of a three-phase sequence of movements (fig. 15).

Fig. 15.

Diagram to show the triphasic nature of the respiratory movements of a lizard (*Lacerta*). Upwards on the thoracic mechanogram is produced by an inwards movement. (Based on Boelaert, R.; *Arch. int. Physiol.* Vol. 51, 1941.)

This can be seen in many lizards where respiration begins with an initial expiratory phase followed rapidly by an inspiration and finally a brief expiratory movement. A pause ensues before the next respiratory act. During the pause the lung is inflated and the glottis closed so that gaseous exchange continues. The gas contained in the lung is held at a pressure which exceeds atmospheric; the initial expiratory movement is an active one

as is the large inspiratory movement which succeeds it. But the final expiration is passive and results from movements of the abdominal viscera which are not separated from the thoracic region by a diaphragm. Ventilation of the lungs themselves is certainly diphasic in character, for the glottis is open at the beginning of the initial expiratory phase and closes before the final passive expiration.

The glottis and nostrils are guarded by sphincters in most lizards. The bucco-pharyngeal movements are frequently found during the long pauses between successive pulmonary movements of many reptiles. The nostril valves play little part in normal ventilation of the lungs but their importance in aquatic forms is much greater. Thus in some turtles which are wholly marine, it has been observed that the nostrils may be filled with highly vascular tissue which plugs them and so prevents the entry of water. When other aquatic turtles come to the surface, very marked peristaltic movements of the throat can be observed and there seems little doubt that the animal is actively ventilating the bucco-pharynx although there are no visible movements suggestive of pulmonary ventilation. In the chamaeleon, the active participation of a buccal force-pump enables the animal to inflate its lungs and air sacs to a large size. Some turtles are said actively to ventilate the pharyngeal cavity when they are submerged and oxygen is absorbed by means of fine filaments which project down from the roof of the mouth. Oxygen consumption of these forms is very low during submergence (7ccs/kg per hour); 30 per cent seems to be absorbed in the bucco-pharynx and 70 per cent through the soft skin. It has recently been shown that some freshwater turtles (*Pseudemys*) can exist on anaerobic metabolism during prolonged diving.

(c) BIRDS

As might be expected from their constant body temperature and great activity, birds have a high metabolic rate (Table 1). This demands an efficient system for gaseous exchange but perhaps unexpectedly the bird lung is a small compact structure

embedded dorsally in the ribs. The bronchial tubes communicate, however, with air sacs which take up a large volume of the body cavity and extend into the cavities of the long bones. These air sacs are not concerned with gaseous exchange as such, for they have a relatively meagre blood supply and carbon monoxide injected into an air sac which has been ligatured from the lung does not get into the general circulation and produce poisoning of the haemoglobin. The precise function of the air sacs remains doubtful although they were first described by William Harvey in 1651. Table 8 gives the percentage of the inspired air which is contained in the lung and different air sacs of the hen. It is apparent that the abdominal sacs are by far the largest cavity of the whole respiratory system, taking between 70 and 90% of the total inspired air. The volume of air inspired or expired in one breath (tidal air) is about 35 to 45 ccs in a duck or chicken and 5 ccs in a pigeon. These figures are only 10 to 15% of the total capacity of the respiratory system and hence only a small portion of the air in the sacs must be expired at each respiration.

TABLE 8

Percentage of inspired air entering different parts of the respiratory system of a Hen (after Zeuthen, 1942)

Lung	up to 4%
Interclavicular sacs	0-1%
Anterior Thoracic sacs	8-15%
Posterior Thoracic sacs	3-12%
Abdominal sacs	70-90%

The trachea is supported by cartilaginous rings and at its base, before dividing into the two primary bronchi, the voice box or *syrix* is found (fig. 16a). Each primary bronchus continues through the middle of the lung as the single *mesobronchus* (1 mm. in cross section), ending posteriorly in an abdominal air sac. From this primary bronchus arise two groups of secondary bronchi. The anterior group arise on the dorsal side of the

mesobronchus although they are frequently referred to as ventro-bronchi. This group of four *anterior secondary bronchi* are amongst the largest tubes of the respiratory system expanding rapidly from narrower origins on the mesobronchus. The third of them communicates with both the anterior thoracic and inter-clavicular sacs whereas the first sends a branch forwards to the cervical air sac. The *posterior* group of *secondary bronchi* (sixteen) arise both dorsally and ventrally from the mesobronchus. The posterior thoracic sacs expand from one of the

Fig. 16.

Diagrams of (a) the main respiratory passages and air sacs of a bird viewed from the left medial side. (based on Akester, 1960.) (b) Cross-section of many parabronchi. (c) A single parabronchus with the air capillaries radiating from its central canal. (after Hazelhoff, E. H. *Poultry Sc.* Vol. 30. 1951.)

posterior bronchi or perhaps directly from the mesobronchus itself. The secondary bronchi of the anterior and posterior groups are joined by a very large number of *tertiary bronchi* (*parabronchi*) which number over a thousand and form the main bulk of the lung. Their path between the anterior and posterior groups varies in relation to the position of their origin. The para-

bronchi are compressed together and diagrammatically they may be represented as hexagons in cross section with an internal tube of about 0.5 mm. diameter (fig. 16c). From the lumen of these tertiary bronchi, fine blind tubes arise which are up to 10 μ in diameter. These *air capillaries* may anastomose and are profusely supplied with blood and it is at their surface that the gaseous exchange takes place. The distances from the parabronchial lumen to the end of the air capillaries are small and both Zeuthen and Hazelhoff calculated independently that diffusion was sufficient to satisfy the birds' requirements, both at rest and in flight.

The mechanism for ventilation of this complex system is basically a *costal suction pump* as in reptiles. The movements are shown diagrammatically in fig. 17; expansion of the thoracic cage is produced by the action of intercostal muscles which move the ribs forwards and outwards while the sternum is depressed and moved slightly forwards. Thus, during inspiration the vertical dimension of the thorax increases greatly and the transverse dimension slightly. The consequent reduction in pressure within the body cavity and pleural cavities results in air being drawn into the system. Expiration mainly results from relaxation of the intercostal musculature but there is evidence for active contraction of the abdominal muscles and internal intercostals. During flight, the rhythmic raising and lowering of the sternum produced by activity of the flight muscles ventilates the respiratory system. It is possible, however, that the bird is also able to ventilate the lung by another mechanism, for it must exhale air continuously when emitting continuous sounds during flight. The respiratory rhythm is unchanged when a bird makes its more rapid flight movements in the laboratory.

The path of the air through the respiratory system during expiration and inspiration has given rise to much conjecture and several theories have been developed to account for the experimental observations. No completely satisfactory solution has yet been found; those features which are fairly definite and common to many accounts will be summarised here, and the two most probable alternatives will be indicated. There is no evidence for the existence of passive flap-valves which might

Fig. 17.

Diagram to show the ventilation movements of the ribs and sternum of a bird. Their position during expiration are shown by full lines. Following activity of the external intercostal muscles the positions shown by dotted lines are taken up during inspiration.

direct the flow along the various respiratory tubes as had been suggested by several authors. Nevertheless, the parabronchial walls contain muscles which by contracting can vary the cross sectional area of the tube and hence vary their resistance. It is almost certain that air passes along the parabronchi during both the inspiratory and expiratory movements. There will therefore be a continuous flow of air past the areas from which the air capillaries take their origin. The absence of dead spaces near the sites of gaseous exchange is mainly the result of the bellows-like action of the air sacs.

The two most probable theories of ventilation differ in their views concerning the direction of air flow during the two phases

of the respiratory cycle. One account (Zeuthen) believes that the air passes through the parabronchi in opposite directions during inspiration and expiration, but the other theory (Hazelhoff) maintains that the direction of flow is the same throughout the whole respiratory cycle and is in the direction from the posterior secondary bronchi to the anterior group. The first theory seems reasonable on aerodynamic grounds, for air coming down the mesobronchus to the point of origin of the anterior secondary bronchi has two possible paths in its passage to the abdominal and posterior thoracic sacs. It can either continue along the mesobronchus or pass via the anterior secondary, tertiary, and posterior secondary system which run in parallel to the mesobronchial path. It is apparent that the volume of flow through these parallel systems will be inversely proportional to the resistances of the two parallel channels. If the flow is laminar, as calculations indicate it probably is, and if the pressure gradient is assumed to be the same across both systems, then, with Poiseuille's formula,* it is possible to calculate the ratio of flow between them. It must be remembered that although the cross-sectional area of each parabronchus is small there are a very large number of them so that the total resistance to movement along this path is not necessarily greater than that of the mesobronchus. Calculations show in fact that within a wide range of variation of mesobronchial diameter there will always be considerable flow through the parabronchi. During expiration, when the posterior thoracic and abdominal sacs are compressed, air will pass in the reverse direction along these two parallel paths in the same proportion if the diameters of the parabronchi and mesobronchi remain the same. Evidence for this type of flow comes from determination of the CO_2 content of the air sacs and the expired air, together with values for the volume of gas entering and leaving the sacs. As the precise CO_2 content of the mesobronchial air is not known, estimates were made based

* Rate of flow = $\frac{P \cdot \pi \cdot R^4}{8 \cdot L \cdot \eta}$, where P is the pressure difference along a rigid tube of length L and radius R . η is the coefficient of viscosity.

upon the CO_2 content of the blood leaving the lung which is the same as that in the systemic circulation. Zeuthen has calculated that during inspiration 29–48 per cent of the air reaches the air sacs by way of the parabronchi. Of the expired air, 38 to 67 per cent passes by the same route.

The existence of a *unidirectional* flow through the parabronchi in an anterior direction was suggested by the aggregation of charcoal at the origin of the posterior secondary bronchi when it was injected into either the trachea or the abdominal air sacs. This observation, and experiments on glass models together with experiments on the movement of fluids in the fixed lung produced by changes in pressure of the tracheal cavity, are the main lines of evidence which support this theory. The suggested mechanism emphasises the importance of a deflector plate on the mesobronchus opposite the point of origin of the posterior group of secondary bronchi. It also supposes that during inspiration air is drawn out of the anterior secondary bronchi by an aerodynamic effect resulting from the rapid flow of air down the mesobronchus, rather like the action of a filter-pump.

As yet the evidence for both theories is inconclusive and until observations based upon X-ray cinematography of the lung are carried out there seems little hope of any final resolution of this problem. Nevertheless, it is clear that the mechanism of ventilation of the lungs by means of a bellows-like action of the air sacs is a very adaptive one and efficient relative to those which utilise a tidal mechanism without the possibility of a continuous renewal of the gas at the respiratory surface.

(d) MAMMALS

The body cavity of mammals is divided into perivisceral, pericardial, and pleural cavities because of the evolution of a true *diaphragm* separating the perivisceral coelom from the thoracic cavities (fig. 18a). This structure is unique, for although similar muscular organs are present in other animals they are not homologous with the mammalian diaphragm. It is dome-shaped anteriorly and is attached to the lumbar vertebrae and posterior

ribs. Contraction of the circular and radial fibres lowers the dome and increases the volume of the pleural cavities. In man this movement is normally about 1.5 cm. downwards and, from its surface area, estimates have shown that its movement can account for nearly the whole of the 500 ml. of air which is taken into the lung with each breath. The central tendon of the diaphragm does not dome upwards so much as the two sides so that during relaxation the right and left sides of the diaphragm are elevated above the central tendon by the abdominal pressure.

The thoracic cavity may be increased in volume by changing its cross-sectional area as a result of the action of the ribs. In most mammals these are inclined posteriorly and ventrally from their articulation with the vertebrae. This articulation is by two heads, the tuberculum and capitulum, and movement is restricted to the axis of their joints with the transverse process and centrum respectively. The external intercostal muscles are attached between the ribs, the attachment to the anterior rib being closer to the vertebral column than the insertion on the more posterior rib (compare fig. 17). These muscles are largely inspiratory in character, and the internal group of intercostals which are used during expiration have a diagonally opposite arrangement. Both diaphragmatic and intercostal activities are sufficient to produce ventilation of the lungs by themselves. Human infants rely entirely on the diaphragm because their ribs are oriented at right angles to the body axis so that any movement of them results in a decrease in volume of the thoracic cavity. Adult females use the intercostal muscles to a greater extent than do males who rely more on diaphragmatic breathing. In quadrupeds which depend on the thoracic cage to suspend the fore-limbs through the shoulder blade, the diaphragm is used to a far greater extent than the rib cage. Correspondingly, aquatic mammals use the intercostal musculature much more because the body is supported by the water. Aerial and bipedal mammals use the intercostals and the diaphragm in a way similar to that of humans.

The lung is contained within the true pleural cavity formed by

the pleural membranes and because of its elasticity and tendency to draw away from the thoracic wall the pressure within the pleural cavity (*intra-thoracic pressure*) is usually 3 to 4 mm. Hg. less than atmospheric (fig. 18b). At rest the pressure within the lung (*intra-pulmonic*) is atmospheric but during inspiration the fall in intra-thoracic pressure results in the intra-pulmonic pressure becoming less than that of the air and consequently air flows into the lung and increases its volume. The pressure within the lung therefore returns to atmospheric and increases still further at the beginning of expiration when the volume of the pleural cavity decreases and the consequent increase in pressure is transmitted to the lungs and reduces their volume.

The total capacity of the lungs in man is about $5\frac{1}{2}$ litres. Even following the most forced expiration $1\frac{1}{2}$ litres or more of this air cannot be forced out of the lungs. The amount which can be exchanged as a result of forced inspiration and expiration is called the *vital capacity*. Normally this lies between 3 and 4 litres but may be 5 to 6 litres in an athlete. The volume of air inspired and expired during normal breathing is the *tidal volume*. An average figure is 500 to 600 ccs. Only part of this air reaches the alveoli, however, as the rest fills the air tubes etc., which lead to the respiratory epithelium. The air contained in these tubes forms the so-called *dead space* which is about 140 ccs and hence the volume of air actually reaching the alveoli at each breath (*the alveolar air*) is little more than 360 ccs. This volume of air which enters the alveolar spaces becomes mixed with some $2\frac{1}{2}$ litres of air that is already present. Consequently, the effect of such a relatively small volume on the composition of the total alveolar air is only slight, probably less than $\frac{1}{2}\%$. For example, the CO_2 content of the alveolar air at the end of expiration is about 5.70%. At the end of the next inspiration it is 5.54%, the slight dilution being produced by the intake of 360 ccs of air. It is clear therefore that the alveolar air may remain relatively constant because of its buffer position between the atmospheric air and the tension of gases in the blood. The whole of the regulatory mechanisms governing respiration are directed to the maintenance of the composition

Fig. 18.

(a) Diagram to illustrate the basic structure of mammalian respiratory systems. (b) The changes in pressure in the pleural cavities and within the lung are shown during a normal respiratory cycle. (b after Ruch and Fulton, 1960.)

of the alveolar air. This constancy contrasts with the marked differences in composition of the inspired and expired air. Inspired air contains 21% of oxygen and 0.04% of carbon dioxide, whereas expired air has only 16.4% O_2 but 4.1% carbon dioxide. This percentage of carbon dioxide increases if a man breathes slowly and deeply because an increasing proportion comes from the alveolar air. With hyperventilation (forced breathing) the CO_2 content of the alveolar air falls and hence that of the expired air.

The gaseous exchange which takes place in the alveoli is greatly facilitated by their enormous numbers. There may be as many as 350 million alveoli in each lung of a man. Each alveolus is less than $\frac{1}{2}\mu$ thick and is only 100μ across.* The total internal surface of the respiratory epithelium is therefore

* Collapse of the alveoli on account of their small size and surface tension forces is prevented by the presence of a thin lining of surface active material.

enormous (Table 1). The lung forms a compact structure, however, as it is supported by the presence of connective tissue which includes many elastic fibres. The elastic tissue is relatively abundant in the finer branches of the bronchial tree but in the larger branches there are quite distinct muscle layers. The cilia on the epithelium permit a constant renewal of the fluid layer through which diffusion must occur. They beat continuously towards the mouth and remove foreign material from the respiratory tract.

(e) DIVING IN TETRAPODS

The ability to spend a greater or lesser amount of time submerged is found in all groups of living tetrapods and is known to have occurred in many now extinct groups. In nearly all cases oxygen continues to be obtained from the air although some neotonic *Amphibia*, which remain tadpole-like when adult, absorb it from the water by means of their external gills. The problems facing poikilothermic divers are not so great as those for homoiotherms because even on land they frequently pass long periods without breathing. In diving birds and mammals, however, the regular respiratory rhythm must be modified if diving is to be longer than the normal period of respiration. Few diving birds are able to submerge for longer than two minutes, although ducks have been kept with their heads beneath the water for at least fifteen minutes and survived when brought up again. Diving times of many mammals are well authenticated and some are given in Table 9. The longest dives are made by certain whales but seals frequently submerge for fifteen minutes or longer. Nevertheless, their average duration may be substantially less than the figures given in this table.

In all cases the diving animal takes down a certain volume of oxygen either in its lung or physico-chemically combined in the blood, muscles, or tissue fluids. The extent of such stores has been calculated for several divers and is given below for a seal, whale, guillemot, and alligator (Table 10). It is noticeable that the site of the major oxygen supply varies for each animal. The seal takes most oxygen down combined in its blood which has a

TABLE 9
Diving times of vertebrates

Seal	15 mins. (normally shorter — 5 mins.)
Beaver	15 mins.
Finback Whale	30 mins.
Sperm Whale	60–90 mins.
Bottle Nose Whale	120 mins. and more
Alligator	15 mins. (experimentally 2 hrs.)
Guillemot	1–2 mins.
Man	2½ mins.

TABLE 10
Oxygen stores of some vertebrate divers. The most important store for each animal is underlined

	<i>Seal</i> (29 kgm)	<i>Bottle-nosed Whale</i> (1400 kgm)	<i>Guillemot</i> (1 kgm)	<i>Alligator</i> (3 kgm)
Lungs	50 ccs	6 litres	<u>40 ccs</u>	<u>51 ccs</u>
Blood	<u>1100</u>	45	<u>18</u>	<u>8</u>
Muscle	<u>270</u>	<u>54</u>	8	1
Tissue fluid	100		4	
Total O ₂	1520 ccs	105 litres	70 ccs	60 ccs

very high oxygen-carrying capacity (29.3 vols. %). Whales have muscles with a very high myoglobin content, as is appreciated from the red colour of their flesh. Birds and reptiles appear to take nearly all their oxygen beneath the surface in the lungs and air sacs. From the total oxygen stores present in the animal before it submerges, and a knowledge of the metabolic rate, it is possible to calculate the time for which the store is adequate. Scholander did this for the seal and, assuming a metabolic rate the same as when resting at the surface, he obtained values of between 5 and 7 minutes. In the case of the bottle-nose whale 15

minutes is a reasonable estimate, but both this and the time suggested for a seal are optimistic, because there is little doubt that the metabolic rate of an animal swimming under water must be greater than during rest at the surface. Allowance has been made for this difference in work on the guillemot where, assuming a resting metabolic rate, the oxygen store was sufficient for 3 minutes but if the animal was swimming at the not unreasonable speed of 2 metres per second, the oxygen would only be sufficient for a 20-second dive.

Many poikilotherms such as the alligator and toad show a reduction in their metabolic rate when they dive and in this way are able to extend the time before their oxygen stores become exhausted. In some cases amphibians hibernate beneath the surface and their oxygen consumption is reduced almost to zero. Some diving turtles also have reduced metabolic rates but others seem to depend almost entirely on anaerobic metabolism.

Although the economic use of their O_2 stores is important, the duration of the dives of some mammals is of a different order from that of the dives of animals which can be sustained solely by this means. The seal is a convenient animal for experimental purposes and Scholander made the following observations when an animal was submerged in the laboratory:

- (i) Air was expired from the lung, which facilitated the dive by reducing the animal's buoyancy and also decreased the danger of Caisson sickness which may result if too much nitrogen is forced into solution in the blood (see p. 64).
- (ii) Almost immediately the heart rate dropped from 150 to 10 beats per minute. Blood samples showed that the oxygen in the arterial blood dropped from full saturation (29 vols. per cent) to about 2 or 3 vols. % which is the danger level.
- (iii) The lactic acid concentration in the arterial blood increased steadily as did the CO_2 tension.

On returning the animal to the surface:

- (i) Air was immediately taken into the lungs;

- (ii) the heart beat rose to normal;
- (iii) there was an increase in the arterial oxygen tension and a fall in the CO_2 tension.
- (iv) The most marked effect, however, was an enormous increase in the lactic acid content of the blood.

This work was the first of its kind and, together with subsequent observations, has suggested the presence of several important physiological adaptations:

- (a) The respiratory centre must be relatively insensitive to the accumulation of carbon dioxide in the blood, for breathing may be inhibited for as long as 15 minutes.
- (b) Anaerobic glycolysis evidently occurs in the musculature, building up an oxygen debt with accumulation of lactic acid.
- (c) Changes in the cardio-vascular system prevent this lactic acid from affecting the whole body. The rate of heart beat is lowered, but in spite of this the mean blood pressure is maintained although the pulse pressure curves change their wave form. These changes in the blood pressure curves indicate the presence of shunting mechanisms in the vascular system whereby the supply of blood to the brain and head is maintained although its flow to the musculature is reduced. *The rete mirabile* found in many parts of diving mammals were at one time thought to represent auxiliary oxygen stores but many of them are now regarded as elaborate arterio-venous anastomoses through which blood can circulate without entering the tissues themselves. A further adaptation in seals is the presence of a sphincter in the inferior vena cava which, if shut during a dive, will decrease very considerably the volume of blood returning to the heart from the viscera.

These mechanisms, then, ensure an economic usage of the oxygen stores of the animal and maintain a sufficient supply of oxygen to the brain. The cutting-off of parts of the peripheral circulation enables the accumulation of lactic acid to proceed

without its harmful effects on the other parts of the animal. On surfacing, the oxygen debt set up during the dive is paid off rapidly, partly because of the efficient respiratory exchange mechanisms but also because of the high oxygen-carrying capacity of the blood. The lung volume is slightly larger in some diving mammals (7% in dolphin, 5% in man and seals) but among whales it is relatively small (2.5%†). The tidal volume is considerably greater in most divers, being as high as 80% of the lung volume in the porpoise (20% in man).

Whether changes similar to those described for seals occur during the diving of whales is not known. There is evidence for bradycardia* but it has not been fully established. One point of difference is that whales fill their lungs *before* they dive. A mechanism for taking in oxygen through the single dorsally placed nostril is very efficient, for a projection from the larynx can communicate directly with the internal nostril and the air need not enter the buccal cavity itself. The external nostril is guarded by elaborate valves so that during the dive the aperture is closed. Many whales dive very deeply and appear to incur dangers well known to human divers such as 'Bends' or Caisson sickness. During a deep dive any air taken down by the animal is compressed and partly forced into solution in the blood. On rising the air is decompressed and the gases tend to come out of solution. Any oxygen coming out of solution is readily utilised in the tissues but nitrogen presents a serious problem. Bubbles of this gas appearing in the tissue fluids or blood vessels can have very serious consequences and may lead to death. Whales differ from human divers supplied with air from the surface as this is continuously renewed, but in a whale a given volume of air is taken down which is initially at atmospheric pressure. Whales in fact take relatively small amounts because their lung capacities are usually between 1 and 3 per cent of the body weight whereas in man the lungs form at least 5 per cent of the weight. Those whales which make longer and deeper dives have smaller lungs. Evidently, then, they take down relatively little air and furthermore the volume of the lung taken up

* Slowing of the heart.

† Litres/100 kgm.

by the non-respiratory surfaces i.e. bronchii, tracheal tubes etc., is quite large (about 1/11th of the total lung volume). Thus at 11 atmospheres pressure the total volume of the lungs will be reduced to that of the inert passages and hence the air will not be in contact with any respiratory surface and the dangers of nitrogen uptake will be negligible. Assisting in the transmission of the external pressure changes from the water to the lungs is the horizontal position of the diaphragm in whales. The reduction in volume to 1/11th occurs at approximately 100 metres and hence once the animal has dived to this depth the danger of nitrogen being forced into solution in the blood does not increase further.

Evidently a whale can stay below this depth so long as its oxygen store and its ability to undergo anaerobic glycolysis can persist. On coming towards the surface it may do so quite rapidly until it reaches the 100-metre depth, but above this its progress to the surface results in the gradual coming out of solution of the nitrogen forced into the blood during the dive. This volume will be slight relative to the blood volume and some nitrogen may be dissolved in the fat. If the whale's progress to the surface is slow there will be little danger of the bubbles of nitrogen forming in any quantity. On surfacing whales have many times been observed to 'spout' which results from the rapid expulsion of air from the lungs and, being hotter than the external air, results in rapid condensation of any moisture contained in it. Between dives the whale rests at the surface, undergoing brief and shallow dives as it pays off the oxygen debt incurred during its longer stay beneath the surface.

Information regarding the physiological adaptations of other vertebrate divers has been obtained recently and indicates that several of the phenomena described for the seal are quite general. Notably the bradycardia following submergence has been observed in ducks, guillemots, birds, snakes, alligators, and also man. Studies on the changes in blood pressure and the pulse pressure curves during diving of the guillemot and alligator have indicated that changes must occur in the resistance to blood flow during a dive. The pulse pressure curves from an alligator when

at the surface and following submergence for three minutes show that the mean pressure remains approximately the same but that the pulse pressure increases during the dive. The rate of rise of the pulse curve is more rapid but its decline is much slower than normal. All these features suggest some vaso-constriction in the circulatory system. After submergence for ten minutes the systolic, diastolic, and pulse pressures all fall quite markedly. Following surfacing of the animal there are increases in the diastolic and systolic pressures but an initial fall in the pulse pressures. It seems clear that in these animals there is an economic usage of the oxygen in the lung and measurements have shown that this falls rapidly during the first 20 minutes of a dive but only gradually during subsequent periods of an hour and a half during which the animal is kept submerged. During normal diving conditions the animal rises after 15 minutes. The changes in lactic acid present in the blood are not exactly as found in the seal, and suggest that the blood supply to the muscles is maintained during the dive. Similar conclusions were reached from the work on the guillemot. During a dive, as well as during recovery, the blood lactic acid increased rather slowly. Similar tendencies were found in the lactic acid content of the muscles and in some cases there was even a decrease in lactic acid content observed at the beginning of the submergence period. The conclusion that the muscles remain open to the blood circulation during a dive seemed inescapable from these and other observations.

In connection with these observations on diving tetrapods it is of interest to recall the response of fish when removed experimentally from water. Inhibition of the respiratory movements occurs in most cases and distinct bradycardia has been observed for many species. For example, in the carp the heart rate falls from 60 to 5 per minute. In the cod, not only was bradycardia observed but also a slow accumulation of lactic acid in the blood which increased suddenly when the fish was once more returned to the water. By the same arguments as those discussed above, we must suppose the presence of some vaso-constriction in the circulation which prevents the flow of lactic acid into the general circulation during the period of asphyxia.

The Metabolic Activity of Vertebrates

The amount of oxygen required by animals varies a great deal but certain general patterns are recognisable. A major difficulty in comparing the metabolic rate of different species is that they have been determined under widely varying conditions of size, temperature, activity, and acclimation (see p. 72), to enumerate but a few of the factors involved. Animals vary in the effect of these factors upon them, to say nothing of their reaction to experimental conditions. Among vertebrates the presence of groups (homoiotherms) which maintain a more or less constant body temperature adds a further complicating factor. Nevertheless the metabolic rates obtained for a wide variety of animals by different methods give a general picture which is surprisingly constant. Unless it is stated otherwise, the figures used in the following sections refer to the resting or 'standard' metabolism, i.e., the oxygen consumption measured for minimal activity.

(a) BODY SIZE AND METABOLISM

In general, birds and mammals have higher metabolic rates than fish, amphibians and reptiles. This is partly because of the higher body temperature of the homoiothermic groups but, even when animals of the same size range are compared at the same temperature, birds and mammals continue to show the highest oxygen consumption. Thus the figures given in Table 11 for the metabolic rates of reptiles and mammals of similar sizes at 37° C. show that mammals respire at about seven times the rate of reptiles. Similar conclusions are reached when comparisons are made between mammals under hypothermia and reptiles at the same temperature. It is difficult to generalise

about the relative oxygen consumption of different poikilothermic groups because it depends a great deal on the mode of life of the individual species. This is also true among warm-blooded vertebrates but when the metabolic rates of members of the same class are related to their size some interesting features emerge.

TABLE 11

Comparative metabolic rates of a reptile and mammals of similar weights (70 grams) at 37° C. (Data of Dawson and Bartholomew, 1956)

	ccs O ₂ /kgm/hr
Lizard (<i>Dipsosaurus</i>)	180
Kangaroo Rat (<i>Dipodomys</i>)	1200
Antelope Ground Squirrel (<i>Citellus</i>)	1300

In a given group the oxygen consumption/unit weight increases inversely with the body weight. In homoiotherms this was thought to be due to the relatively greater heat loss from smaller animals. The latter have a relatively larger surface from which heat may be lost and might therefore be expected to consume more oxygen in maintaining a constant body temperature. This has given rise to the so-called *surface area law* which suggests that the metabolic rate is proportional to the surface area of the animal. Over a limited range this appears to be true, e.g., animals such as the hen (2 kg.), dog (15 kg.), man (65 kg.), and pig (130 kg.) all have metabolic rates of about 9 ccs O₂/sq. metre/hour. But such a relationship does not hold for the entire size range of vertebrates. The formula best fitting all the data is given by the relationship:

Heat production or metabolic rate $\propto$ (body weight)^{0.73}.

It is generally believed that:

Surface area $\propto$ (body weight)^{0.66}.

However, the loss of heat in warm-blooded vertebrates can occur from areas other than the external body surface, e.g., the lungs, so that if it could be shown that:

The surface area for heat loss $\propto$ (body weight)^{0.73},

then it would be valid to accept the surface area law.

The metabolic rate of small birds and mammals (fig. 19) rises very steeply with decreasing size. It would be extremely difficult for a mammal weighing less than 3.5 grams to obtain sufficient food to maintain its activity. Furthermore, the strain on the circulatory system in such animals becomes extremely acute and it is notable that this increase in metabolic rate is

Fig. 19.

Graph showing the relationship between body weight and metabolic rate in some small mammals (After Pearson, 1957).

correlated with an increase in the percentage heart weight and a pulse rate which, in small birds, may exceed 1000/minute. The amount of work done by the heart in pumping sufficient blood round the circulatory system in unit time becomes considerable. One factor affecting the lower limit to size of homoiotherms must undoubtedly be the difficulty of keeping up adequate supplies of oxygen to the heart at these extremely high metabolic rates.

The factors of heat loss and heart size, however, cannot be the full explanation of the relationship between metabolic rate and (body weight)^{0.73}, for similar relationships hold in poikilotherms. This is true not only of vertebrates but also of a very wide range of invertebrates; even single egg cells obey a similar relationship. Zeuthen found that the power of the body weight to which the metabolism is related varies in different groups. The situation is extremely complex and cannot be adequately interpreted in terms of a single relationship. He pointed out that animals can either be small, grow rapidly, and live intensely, or they can be large, grow slowly, and metabolise at a low rate. Between these two, however, many intermediates are possible.

(b) METABOLIC RATE AND TEMPERATURE

Most chemical reactions are influenced by temperature in such a way that the velocity increases with rising temperature. In living organisms most reactions are catalysed by enzymes and over a certain range they behave in a similar way. However, above a certain temperature the enzyme, being largely protein in nature, becomes inactivated and consequently the rate of reaction declines. The result of these two opposing effects leads to the existence of an optimum temperature at which the rate of a reaction is most rapid. For most enzymes it lies between 30° and 40° C., and because this is also the range of body temperature found in mammals and birds, it has been suggested that their temperature is that at which the enzymes function most efficiently. The range of body temperatures over which animals can survive is roughly from 0° to 50° C., which again coincides with the range of activity of most enzymes.

Most chemical processes which take place in living organisms follow an exponential curve such that the rate of the reaction is doubled or trebled for a rise of 10° C, i.e., $Q_{10} = 2 - 3$. The effect of temperature on the metabolic rate of poikilotherms also tends to show a similar relationship. Most terrestrial animals have an upper lethal temperature of about 45° C. Such temperatures can be survived very briefly so that if the time of exposure is taken

into account the upper lethal temperature is five or more degrees lower. It is likely that denaturation of the proteins is involved at these temperatures but this cannot be the case in arctic fish which may have upper lethal temperatures as low as 10°C .

(i) *Poikilotherms*

Although the metabolic rate of cold-blooded animals follows the environmental temperature this is not to say that there is no control at all or that they are always cold. They do not have exactly the same temperature as the environment, especially when this is fluctuating. Smaller individuals follow the air temperature with less time lag than larger forms which tend to maintain a temperature which is the mean of any fluctuations in the environment. One effect of this is that small poikilotherms are able to take advantage of brief periods of sunlight to become warmer. Many reptiles bask in the sun early in the morning, burrow later in the day to avoid excessive heat, reappear again in the cool evening and finally burrow again as it becomes cold during the night. At the cold end of the range a serious danger is that freezing of the body fluids may lead to death because of the effects of ice crystal formation disrupting the protoplasmic structure, especially during warming-up. Some small animals may be frozen and survive de-freezing but few adult vertebrates are in this category, though mammalian sperm and red blood cells can be stored when frozen for many months if pre-treated with glycerol, frozen quickly, and stored below -40°C . Hamsters have been maintained frozen at temperatures of -3° to -14°C . for more than 50 minutes and survived when warmed gradually and given artificial respiration. Some arctic fish are known to live in waters with temperatures of -1.7°C . although the freezing point of their blood is -0.9°C . If fish under such conditions are seeded with ice crystals they freeze at once and it is evident that the blood is in a super-cooled state. Fishes inhabiting the deep fjords of Labrador do not normally come into contact with such crystals and in this way survive the low winter and summer temperatures. Those living at the surface, however, live in temperatures of 5°C . in summer and -1.5°C . in winter. It

appears that in winter the blood contains some unknown solute which lowers its freezing point from -0.8° in summer to -1.6° in winter.

Despite the relative paucity of their regulating mechanisms, poikilotherms do have some control when considered over long periods. For example, animals which live under cold conditions usually have a higher metabolic rate at that temperature than closely related species, or individuals of the same species living under warmer conditions. This capacity of living organisms for modifying their metabolic rates to meet the conditions under which they normally live is referred to as *acclimation*. Fig. 20a shows the relationship between metabolic rate and temperature in a species which does not show any acclimation; the curves for

Fig. 20.

Metabolic rate of poikilotherms at different temperatures, (a) without any acclimation, (b) showing acclimation. The curves for individuals from warm conditions are shown by full lines (w) and the dashed lines are for those living in cold environments (c). The dotted line indicates the relationship for an animal subjected to changes that are sufficiently slow for it to be acclimated at all temperatures (After Bullock, T. H.: *Biol. Revs.* Vol. 30, 1955.)

individuals normally living at higher and lower temperatures are continuous with one another. In most instances, however, the two curves would be different (fig. 20b); the curves for tropical forms being below those for arctic fishes at the temperature range $0-10^{\circ}$ C. At the normal temperature of their habitat (0°), arctic aquatic forms have metabolic rates which are 3 to 4 times less

than tropical species at their normal habitat temperature (30°C). Extrapolation of the tropical curve gives values at 0°C . which are 30–40 times lower than those at the normal tropical temperature. This indicates, therefore, that the metabolic rate of the arctic forms is ten times the value expected had there been no acclimation. Such acclimation is rare among terrestrial species. The precise relationship between the acclimation temperature and the animal's metabolic rate is complex and varies from species to species. The general conclusion is that poikilothermic animals do have ways in which they are adapted to changes in environmental temperature, especially long-term changes. The limitations on their geographical distribution, therefore, are not as great as might have been expected.

(ii) *Homoiotherms*

Among homoiothermic animals the effect of a lowered environmental temperature is to increase the metabolic rate and so raise their heat production and contrasts with the decreased oxygen consumption found amongst cold-blooded forms. There is, however, a range of temperature (the neutral range = 27° – 31°C . in man) over which there is no change in metabolic rate with environmental temperature. Above the thermo-neutral range the oxygen consumption rises just as it does below it. The temperature below which an increase in metabolic rate occurs is referred to as the critical temperature (T_c). This is lower for animals which live in arctic conditions partly because of their large size but also because of their thick coats. In general small mammals live in tropical regions to which they are acclimated and have higher critical temperatures. Mammals with lower critical temperatures have less steep temperature/metabolism curves, i.e., the increase in metabolism for a given fall in temperature is less for arctic forms than tropical forms. Thus the air temperature can only be reduced to 28°C . before the racoon increases its metabolic rate in order to maintain its body temperature, whereas an Eskimo dog pup maintains a constant body temperature until that of the environment falls as low as -25°C .

Fig. 21.

The body temperature of a reptile and some mammals at different environmental temperatures (after Martin, C. J.: *Phil. Trans. Roy Soc. Lond.* Vol 195, 1902.)

The relationship between external temperature and body temperature of different types of mammal is shown in fig. 21. It is apparent that a eutherian mammal, like a cat, is able to maintain its temperature near 37°C . for a considerable lowering of environmental temperature. In the monotreme, *Echidna*, regulation is not so good and the body temperature falls some five degrees when that of the environment is lowered from 35° to 5°C . Monotremes, some marsupials, and forms like the Sloth and Anteater amongst the eutherian mammals tend to have relatively low body temperatures (27° – 32°C .). In these and others, sometimes called *heterotherms*, the range of body temperature compatible with normal activity may be quite large, e.g., hedgehog, 31.1° – 36.7°C .; dormouse, 31° – 38°C .; opossum, 29.3° – 37.8°C . In marsupials, the

Fig. 22.

Oxygen consumption of a humming bird and a shrew throughout a 24-hour period (after Pearson, 1957).

homoiothermic condition is not reached for several months. During its pouch life (65 to 70 days) a change in environmental temperature from 20° to -10° C. leads to a lowering of the internal body temperature by as much as 20° . In the adult similar changes do not affect the deep body temperature at all.

Perhaps the most striking variations from homoiothermy are found in small mammals and birds which are unable to maintain their body temperature when that of the environment falls at night. The humming bird is a well-known example and in fig. 22 the oxygen consumptions of a humming bird and a masked shrew of approximately the same size are plotted for 24 hours. During the night the external temperature falls and the metabolic rate of the shrew increases slightly. The humming bird on the other hand shows a very marked drop in oxygen consumption associated with a fall in body temperature near to that of the environment. In the middle of the night it was living at a metabolic level only 1/15th as rapid as during the day. In this *torpid* state the

animal was practically insensible and scarcely moved, and this represents a considerable metabolic economy over the 24-hour period. It also enables the animal to conserve a great deal of body water. Shortly before daybreak the body temperature spontaneously returns to normal, as does the metabolic rate, and the bird is soon searching for food. Similar torpidity is found in bats, poorwills (a desert bird), and swifts; the body temperature of the bat being almost the same as the environment when it is asleep during the day.

(iii) *Hibernation*

The state of torpor is very similar to that of hibernation found in many mammals and some birds. Hibernation must be distinguished from the deep winter sleep of bears and other large mammals for in the latter the body temperature may be held at 31° – 34° C. although the surrounding air is at -25° C. True hibernation involves a marked change in the temperature regulating mechanism and affects the whole metabolic activity of the animal. Not only does the body temperature fall but also the metabolic rate, heart rate, and respiration, as shown below for a Marmot.

	Non-hibernating	Hibernating
Body temperature ($^{\circ}$ C.)	34–39 $^{\circ}$	3–8 $^{\circ}$
Basal Metabolism (Cals/sq.m./24 hrs)	410	27
Heart Rate/min	80	4–5
Respiratory Rate/min	25–30	0.2

The entry into hibernation may be gradual but in some ground squirrels it has been shown to be a complex process which may take 21 days. The plot of brain temperature shown in fig. 23 indicates the way in which the diurnal lowering of temperature during the night is made use of in this respect. By a series of 'test drops' the temperature on alternate nights is successively

Fig. 23.

The brain temperature recorded from a ground squirrel as it begins to enter hibernation (After Strumwasser F.: *Am. J. Physiol.* Vol. 196, 1959).

lowered from 37° – 35° – 30° – 27° – 23° before the animal enters hibernation. It is apparent that by this mechanism the condition of the overall metabolic control is being tested in order to see whether it is all co-ordinated for entry into this quite new state. During hibernation the temperature is low but is maintained quite accurately at a given level, in some cases $\pm 0.05^{\circ}$ C. of a temperature several degrees higher than the environment. While in hibernation the nervous system retains a certain amount of activity although the cortical waves may be lost in the hamster. The ground squirrel *Citellus* still shows cortical waves of 10/second but reduced amplitude at 5° C. It can localise sounds as well as make small sounds itself when slightly disturbed at brain temperatures of 6.1° C.

Arousal from hibernation is a relatively rapid process and is associated with an enormous increase in oxygen consumption. In hamsters, the metabolism may increase 2–4000 times as the temperature rises to 37° C. within two hours. It is apparent that the whole state of the organism during hibernation is a special

one and certainly cannot be regarded as a return to a poikilothermic condition.

Aestivation has long been used to describe the state of summer dormancy found in mammals and other animals. It occurs particularly as an adaptation to seasonal drought (e.g. in deserts) rather than seasonal cold and is an effective mechanism for surviving periods when food and water are scarce. Several examples have been recently investigated which show that hibernation and aestivation are the same physiological phenomenon. Thus in the Mohave ground squirrel aestivation is characterised by:

- (a) body temperatures within a degree of environmental temperature
- (b) O_2 consumption very low
- (c) absence of breathing for long periods
- (d) torpor deeper than normal sleep
- (e) enhanced O_2 consumption and activity of heat production mechanisms during arousal.

The Control of Respiration and Body Temperature

(a) RESPIRATION

As with other rhythmic motor activities, the control of respiratory movements involves two sorts of problem. The first is concerned with co-ordination of the many different muscles which produce the respiratory movements. Each of these can vary the strength of its contraction and must function at a particular phase of the cycle, otherwise the whole system would become disco-ordinated and ineffective. The second problem is one of regulation, i.e., the way in which the respiratory mechanism adjusts to changes in environmental conditions both within and outside the body. This usually involves modifications of the rhythm and ventilation volume. It is difficult always to separate these two problems but once it has been established how the rhythm is produced, then mechanisms which modify the extent and frequency of its action can be more readily understood.

When considering the determination of rhythmic muscular activities the nervous system can be considered in two parts, the central nervous system and the peripheral input from sense organs. That these two cannot be independent is clear, but the precise ways in which they interact and their relative importance are variable. Three main theories (fig. 24) have been proposed for respiration: (i) The rhythmic movements are determined and controlled entirely by the nature of the sensory inflow to the c.n.s. This reflex view supposes that all movements result from stimuli arising from preceding movements and is no longer strongly held for respiration, as it omits the rhythmic properties

which are known to be intrinsic to most central nervous systems. (ii) Other workers stress the latter properties and suppose that the rhythm is generated by periodic inhibition of the continuous discharge of neurones which innervate inspiratory muscles. This inhibition could come either from other regions of the brain or from inputs derived from the movements themselves. (iii) An even more central view considers that the rhythmicity results entirely from intrinsic properties of the region of the c.n.s. most concerned with respiratory control and that inputs from the peripheral sense organs serve only to modify or regulate the rhythm.

Fig. 24.

Diagram of three possible mechanisms for the generation of the respiratory rhythm in the medulla of a vertebrate. The influence of the input from O₂ receptors and proprioceptors excited by the movements have a driving action in (i), but in (ii) it serves to inhibit a tonically active inspiratory centre. In (iii) the rhythm is generated entirely by the interaction of spontaneously active $\sim$ medullary neurones but it is influenced by the inputs from peripheral receptors and centres in other parts of the brain. The respiratory neurones are sensitive to changes in CO₂ tension of the circulating blood.

Evidence that neurones concerned with respiration lie within

the medulla has been derived from experiments in which electrodes were used for either stimulation, recording, or localised destruction of the so-called respiratory centre. Electrical stimulation of more ventral parts produces inspiration whereas the more dorsal and lateral regions are concerned with expiration. Recording shows a similar distribution of active units although it is by no means as clear-cut as has often been supposed. On this view, which has been generally accepted until the last few years, the inspiratory centre is thought to act tonically (i.e., to have a continuous output of impulses) not only on the lower motor neurones which produce the movements of respiration, but also on the expiratory and pontine or pneumotaxic centres. The latter is a centre within the *pons** which acts back on the inspiratory centre and produces periodic inhibition of the tonic outflow to the inspiratory muscles. Similar inhibitory effects, terminating inspiration, can be produced by the expiratory centre and by the inflow from the vagus nerve which contains sensory fibres from proprioceptors in the lung (probably unencapsulated endings of the tracheobronchial tree). Cutting the vagi does not abolish the respiratory rhythm so this input is not essential for its expression. When the brain is cut in the upper brain stem, following bilateral vagotomy, the animal enters a state of inspiratory spasm or apneusis. This had previously been thought to be due to the removal of the periodic inhibition derived from the pontine or pneumotaxic centre and hence the inspiratory muscles received a continuous discharge of impulses.

One of the main difficulties in accepting this theory is that the so-called apneusis (meaning breath-holding) is apparently not a complete inspiratory cramp but is made up of a series of very small breaths. It is clear, therefore, that rhythmicity persists within the medullary centres even after they are separated from the pneumotaxic centre and from the vagal input. Further evidence for this view came from many experiments in which it was possible to restore normal breathing following these opera-

* A projection from the under surface of the medulla below the cerebellum.

Apparently there is a region in the caudal two-thirds of the pons which must be present if apneustic breathing is to persist and it has been called the *apneustic centre*. Removal of this centre reduces the inspiratory cramp and leads to the development of a more normal respiratory rhythm. The centre is apparently located diffusely in the network of intermingled fibres and cells which comprise the reticular formation rather than in a clearly-defined group of cells within the pons.

It has been concluded that the fundamental respiratory rhythm can develop within the medulla without the assistance of reflex excitation or stimulation from higher centres. It is spontaneously periodic (i.e., comes in bursts in the absence of any input), does not require any sensory input to produce successive alternation of inspiration and expiration, nor does it require the inhibitory effects from the pontine centres. Evidence for this medullary autonomy is also derived from isolation experiments, such as those of Adrian and Buytendijk on the goldfish. They recorded slow rhythmic potentials of about the same frequency (20–60/min.) as the fish breathing movements. Recently, similar slow potential changes have been recorded from intact specimens. Evidence for the central autonomy has also been derived from experiments in which unit activity recorded by fine electrodes within the medulla has been shown to persist when all cranial nerves were cut except the trigeminal (V) nerve on one side. Moreover, after cutting this nerve it was still possible to record bursts of action potentials from the sites where they were present in the whole animal preparation. Similar observations have also been made on the mammalian medulla. In other experiments with mammals and fishes the respiratory movements were abolished by the injection of curare-like drugs which block neuromuscular transmission. Consequently the afferent inflow normally produced by these rhythmic movements was cut off, yet rhythmic bursts of impulses from the motor neurones continued.

These bursts do not persist for long periods, so it appears that some non-specific input to the medulla is necessary for the full expression of the respiratory rhythm.

Nowadays the medullary respiratory centre is not regarded as being composed of distinct inspiratory and expiratory centres although there are certainly neurones which are more active during one or other of these two phases. These units are distributed throughout the medullary region, however, and intermingle with one another. The evidence for the two centres derived from stimulation experiments is difficult to interpret because of the problem of localising the stimulus, which is also unnatural because it produces a synchronous discharge of many neurones.

It may be concluded that the genesis of the respiratory rhythm is due to the interaction between the medullary neurones and the interplay of descending impulses from the pontine regions but may require some non-specific afferent input for its continuous expression. This accords well with the general views derived from recent studies on motor rhythmicity of other types, e.g., the swimmeret rhythm of crayfish.

(b) CHEMICAL REGULATION OF RESPIRATION

It is known from the classical works of Haldane that the CO_2 content of the blood and alveolar air plays a dominant role in the regulation of respiration in mammals. Many mechanisms interact to maintain the composition of the alveolar air remarkably constant over quite a wide range of conditions. Minute increases in the CO_2 content of the alveolar air (e.g., 0.25%) lead to a very marked increase (100%) in the volume of air breathed. Lowering of the alveolar CO_2 by breathing as deeply and rapidly as possible results in a cessation of breathing and a return of the CO_2 tension to its normal level. The ability to hold one's breath, e.g., during diving, is increased by such a preliminary hyperventilation. Above certain concentrations (10% of inspired air) the effects of CO_2 become harmful, anaesthetic, and finally fatal above 40%. During resuscitation of a drowned or asphyxiated person a mixture of 95% O_2 and 5% CO_2 was formerly used. Nowadays the CO_2 is omitted because it would probably have a tension less than that already in the blood,

which would be at least sufficient to produce very marked excitation of the respiratory centre and may even be high enough to have a depressant effect.

The carbon dioxide has a definite effect on the medullary respiratory centres – a notable observation being that a medulla that has been completely cut off from all sensory input and which is more or less electrically silent shows well-defined respiratory potentials when the air mixture ventilating the animal is raised in CO_2 content by 6.5%. Chemical stimulation can also be obtained by the direct injection of sodium bicarbonate and CO_2 into the medulla. The localisation and precise nature of the responses to these injections vary not only in a mammal but also in a teleost fish. Whether the CO_2 has its effect *per se* or because of the resulting changes in hydrogen ion concentration has long been discussed. A recent view is that the effects are the result of both of these. Injection of acid alone certainly stimulates respiration, but the effects on respiratory activity of equal increases in acidity produced by CO_2 inhalation and acid injection show that CO_2 has a greater effect than that resulting from the change in pH alone. It is concluded, therefore, that CO_2 has its effect as a result of both factors.

Chemoreceptors are also present in the carotid and aortic bodies or glomi. These are to be distinguished from the pressor receptors in similar regions (carotid sinus) which also have an effect on the respiratory rhythm but not so marked. Both the carotid sinus and glomus lie close to the bifurcation of the common carotid in mammals; the glomus lies on the occipital artery and the sinus on the internal carotid. The sensory fibres from both pairs of receptors pass to the medulla in the glossopharyngeal (IX) nerves. The aortic glomus is single and lies on the concave side of the aorta. It has similar receptors to the carotid glomi but its afferent fibres enter the depressor branches of the vagus.

Perfusion of the carotid glomus with Ringer solution at constant pressure showed that an increase in respiration followed a decrease in oxygen tension, increase in carbon dioxide tension, or an increase in hydrogen ion concentration of the

fluid. The carotid glomi have a high rate of oxygen usage and it is probable that the accumulation of anaerobic metabolites during O_2 lack is the effective stimulus. The carotid and aortic bodies are relatively insensitive to CO_2 which is mainly detected by the medullary centres but they play a very important role when the O_2 tension of the blood is reduced, e.g., when the inspired air contains less than 14% O_2 .

The sensitivity to CO_2 of the respiratory centre of aquatic mammals is less than that of terrestrial forms. In this way they are able to dive and hold their breaths for longer periods. In fish the respiratory centre seems to have properties similar to that of mammals, and among forms living in well-aerated conditions the sensitivity to CO_2 may be greater than that of forms living in swamps where its tension may be high. Adaptations to an increased CO_2 tension in the blood seem to be a necessary prerequisite for the coming on to land. Most fish so far investigated show an increased ventilation volume in response to both decreased O_2 and increased CO_2 tensions. The responses increasing ventilation in environments containing high levels of CO_2 but normal levels of O_2 appear inappropriate, since they will not apparently lead to an increased oxygenation of the blood. Here we see one fundamental difference between a gill and a lung which arises from the greater difficulty of monitoring the CO_2 tension in the water passing away from the gills. In a lung the CO_2 persists in the alveoli and serves to govern the whole regulatory mechanism. Oxygen tension affects both fish and mammalian regulation chiefly through receptors placed in the aortic arches but also possibly in the gills of fishes. Cutting the 9th and 10th nerves which innervate the gill epithelia produced a decreased response to reduced O_2 tensions in tench. The whole question of regulation of respiration in fishes has not received the attention accorded to mammalian breathing and remains in a much vaguer state. Nevertheless the general organisation is similar, i.e., a medullary respiratory centre of distributed expiratory and inspiratory neurones able to generate the rhythmic activity and which are influenced by CO_2 tensions in the blood.

(c) TEMPERATURE CONTROL

In Chapter 6 we saw that warm-blooded or homoiothermic animals (birds and mammals) maintain body temperatures which are independent of the environmental temperature. This contrasts with poikilotherms, which are far less able to protect themselves against thermal stresses and do so mainly by escaping from them or by other forms of behaviour. The temperature of a mammal does vary, however, and cannot be given a fixed value. Not only does it vary from time to time but also in different parts of the body. Thus in man 98.4°F . and 99.4°F . * are often considered the normal oral and rectal temperatures, but in fact they may range from $98\text{--}99^{\circ}$ and $99\text{--}100^{\circ}$ respectively. These variations may result from feeding and other causes. Furthermore there is a normal diurnal rhythm, the lowest temperatures being recorded between 6 and 7 a.m. and the highest some twelve hours later. The maintenance of this more or less constant body temperature is the result of the interaction of processes concerned with heat loss and heat production. There is an environmental temperature at which both of these problems are most economically accomplished which for man is around 86°F . At this temperature he is able to lose to the environment all the heat formed by his basal metabolism and retain only that which is necessary to maintain his normal body heat, and there is no need to call upon reserve mechanisms of heat loss. The temperature is a little high for his comfortable every-day life, however, for he cannot easily dispose of any extra heat produced during muscular exercise or assimilation of food.

(i) *Heat production and conservation*

The mechanisms of heat production involve the heat liberated from chemical processes within the body, many of which take place within the liver, but they are most readily controlled by adjustments of muscular activity. Voluntary exercise such as stamping the feet, swinging the arms, etc. is one method, but

* 36.9°C . and 37.4°C .

involuntary mechanisms involving an increase in muscular activity which may be asynchronous in individual muscle fibres are also important. The most notable method of course is that of shivering which occurs as a reflex when the temperature of the body falls by $0.5\text{--}0.7^{\circ}\text{C}$. and which is capable of more than doubling the basal heat production. In addition to these mechanisms involving muscular activity there are certainly mechanisms for increasing the basal metabolic heat production by direct effects upon the chemical mechanisms of the body. One obvious means of increase would be to make some of the metabolic pathways less efficient, so that more energy is lost as heat and not transferred from one system to another. Various suggestions have been made which include those of enzymatic shunts in phosphorylation (see p. 130) whereby less ATP is produced and a greater amount of heat liberated.

A notable example of the importance of increased heat production through raising the basal metabolism is that of acclimated white men when sleeping in the cold. Before acclimation they were restless and did not raise their basal metabolism and in consequence the temperature of their extremities fell during the night. Following acclimation the foot temperature remained fairly constant but the basal metabolism was nearly doubled and they were able to sleep quite well. In contrast, Australian aborigines slept well at a normal level of basal metabolism despite a marked fall in their foot temperatures.

Many of the adaptations for heat conservation involve structural features which insulate the body against rapid changes of external temperature. The insulation provided by fur is proportional to its thickness and during winter many arctic mammals increase the thickness of their coats. A large volume of still air enclosed by the fur decreases the heat lost by conduction and convection. The increases in insulation are greater for large mammals (black bear, 52%) than for small mammals (deer mouse, 21%). Fur is also a barrier to the gain of heat, e.g., the camel increases in temperature considerably following shearing. This animal is able to tolerate wide fluctuations in body temperature ($34^{\circ}\text{--}40^{\circ}\text{C}$.) and this must be regarded as a genetic

adaptation to life under these conditions. In water the insulation properties of fur are markedly reduced and in aquatic mammals are replaced functionally by blubber beneath the skin. In seals the skin temperature is only slightly above that of the surrounding water but the visceral temperature is maintained at 37°C . Circulatory adaptations are important in aquatic homoiotherms, for the temperature of the flippers and legs may be ten degrees below the temperature of the main body. This is maintained by heat transfer across a counter-current exchange system between the afferent and efferent blood flows into the distal extremities (fig. 25). In this way the extremities continue to receive their oxygen but get less heat from the body as it would be dissipated at their surfaces.

Fig. 25.

Diagrams to show (a) the juxtapposition of the afferent and efferent blood vessels to the fins and flukes of a porpoise. Each artery is surrounded by a multiple venous channel. (b) The counter-current mechanism ensures a conservation of heat (after Scholander, 1958).

(ii) *Heat loss*

Loss of heat is normally accomplished by three physical processes, radiation, conduction, and the vaporisation of water. At normal environmental temperatures most heat seems to be lost from mammals by radiation and conduction from the body surface, and relatively small amounts are lost by evaporation. Radiation accounts for 60% to 65% of the total loss from man in environments of 70°–80° F. It involves the transfer of heat from the surface to every relatively cool object in the vicinity—furnishings, walls, the ground, etc. Conduction is less important, and includes heat transferred from surfaces in contact with the air—the air covering the skin, clothing, and the tidal air warmed in the respiratory passages, in addition to that transferred to physical objects with which the body comes into contact from time to time. Evaporation removes heat because of the latent heat which requires about 0.6 kcal. for the evaporation of each gram of water.

The proportionate loss by these three processes changes with temperature and mainly in the relative amounts lost by radiation and evaporation. Above 31° C. the amount lost by evaporation exceeds that due to radiation and below this temperature radiation is the predominant factor. In cool air man loses one litre of water per day by evaporation and during hard work in the desert it may be as great as 1.6 litres per hour. Output of sweat increases by 20 grams/hour for each 1° C. rise in air temperature. Many mammals lose heat by panting, e.g., dogs and cattle, whereas others such as the cat and the marsupial, *Opossum*, salivate and lick their fur when heated. Dogs rely a great deal on panting and the frequency of their respiratory movements may be increased from between 15 and 30 breaths/minute to 300/minute at higher temperatures. Most mammals are less efficient than man at increasing their loss of heat by evaporation at high temperatures and their body temperature rises accordingly. This adaptive feature of man's physiology may be related to his origin under tropical conditions.

Among birds the very large surface area of the air sacs leads

to substantial losses of heat from the respiratory tract. Although birds pant to some extent, they have no sweat glands and cannot lose water by that route. Mourning doves pant when their body temperature rises and at air temperatures of 39°C . they consume four times more water than at 23°C . In small birds the water loss may be enormous (a wren loses almost 40% of its body weight per day as water) and in the smallest forms with the highest metabolic rates the loss of water may be a factor limiting their survival. In some humming birds the loss through the respiratory tract must approach 75% of the body weight per day. Small mammals also have similar problems because of their high metabolic rate and relatively large surface areas. Many small rodents have no sweat glands and do not pant, but avoid the heat by living in burrows beneath the desert. Many are nocturnal in their habits but a notable exception is the antelope ground squirrel which inhabits the Mohave Desert of California. This squirrel has a broad thermal neutral zone, for between temperatures of 90° and 107°F . its metabolic rate remains virtually constant. No other non-sweating mammal has a zone which extends so high in temperature. In the absence of sweat-glands it goes in for drooling, i.e., it spreads saliva over its cheeks and head with its paws in order to reduce the body temperature. Fortunately this mammal has an extremely efficient kidney and can withstand considerable dehydration.

(iii) *Nervous mechanisms*

The nervous control of temperature regulation is based upon information derived from receptors which detect a steady level as well as changes in body temperature. Many are found in the skin but it has recently been shown that receptors in the hypothalamus of the fore brain are of great importance in triggering the effector mechanisms which regulate the temperature. In addition to its receptive function, the hypothalamic centre is also the prime thermostat of the mammalian body.

Using special methods, the total energetic output from the skin has been determined regardless of the position of the subject. Heat carried from the body by evaporation was also

measured and the proportions of total heat lost by various routes were established. In this way the activity of the effector side of the control system could be rapidly and accurately measured. Temperatures of the body were determined with thermocouples in the rectum, skin, and in the head at several places only an inch away from the hypothalamus. Continuous measurements at these points showed marked differences between temperatures in the head and those of the rectum and skin. The discrepancies existed during rest, after exercise, and following eating of ice or hot fluids. It is clear, therefore, that the rectal temperature does not give a good indication of the fluctuations at the hypothalamic receptors. This observation is significant because rectal temperatures had previously been used to show the absence of a correlation between internal temperature and the heat-regulating mechanisms. On this basis the role of the hypothalamic receptors appeared to be a subsidiary one. In the light of the temperature measurements in the region of the hypothalamus itself, it was therefore necessary to repeat these observations, using the hypothalamic conditions as an indicator of the internal temperature. These experiments demonstrated the marked correlation between temperature at the hypothalamus and the output of the regulating mechanisms. This can be seen in fig. 26 which shows the changes in head temperature and skin temperatures, together with the heat loss through evaporation and by vaso-dilatation of the skin. Ice was taken by the subject at three points and a marked correlation is seen between the fall in internal temperature and the heat lost by the effector system. Another striking feature is that following the consumption of ice the skin temperature showed a distinct rise of about 0.6°C . Evidently the lowered internal body temperature affects the hypothalamic receptors which stimulate the thermostat which decreases the evaporative heat loss by reducing the sweat-gland activity. The consequent drying of the skin produced the rise in skin temperature. It appears that for these heat-controlling responses the internal receptive mechanism provides more adequate information to the thermostat about heating conditions of the body than would a receptive mechan-

Fig. 26.

The internal temperature near the hypothalamus of a man falls after eating ice. Simultaneous recordings of the sweating from the skin and the heat loss are shown to follow this curve very closely. The skin temperature, however, shows a marked increase when ice is eaten (after Benzinger, 1961).

ism based upon skin sense organs. The latter are important for the production of more conscious temperature control, which frequently results in movement either of the extremities alone or of the whole animal to a warmer environment.

The hypothalamus, then, contains the sensory system which detects temperature changes of the blood circulating through the brain and puts into action those mechanisms which increase the loss of heat from the body. It is triggered at a particular temperature ($36.9^{\circ}\text{C.} = 98.4^{\circ}\text{F.}$) which it tends to maintain with surprising accuracy. Localised electrical stimulation or warming of the anterior part of the hypothalamus produces the expected thermo-regulatory responses. Removal of this part of the brain leads to marked fluctuations in body temperature. The mechanisms whereby the loss of heat from the body is decreased under

conditions of lowered external temperatures have not been elucidated with the same precision, partly because localised cooling is not so easy to achieve experimentally.

Acclimation (i.e., short-term effects, as distinct from acclimatisation) to sudden lowering of temperature is mainly produced by increases in body metabolism but these are usually preceded by responses which restrict heat loss. The increased metabolism is only a temporary solution found in animals not normally subjected to long-term lowering of the external temperature. The more immediate responses probably result from stimulation of cold receptors in the skin. Reflexes take place which tend to conserve heat, e.g., the constriction of the skin capillaries, raising the hair or feathers which increases the thickness of the insulating layers, and the animal may move its limbs about or change its position in order to reduce the heat loss. Only at a later stage does the increased heat production within the animal take place, mainly by increases in muscle activity which eventually lead to shivering. The adrenal cortex and thyroid may also become involved because of their effect on metabolism. A rat regulates its body temperature down to environmental temperatures of -10°C. , but in the absence of the thyroid or adrenal it can only regulate down to -2°C. ; in the absence of both glands the temperature is only adjusted when the environment falls to 10°C.

Transport of the Respiratory Gases

After the oxygen has been absorbed at the respiratory surface it must pass to the cells where the oxidative processes take place. Diffusion of oxygen in water and in the body fluids of an animal is a relatively slow process (Table 2). It can be calculated that to provide oxygen at the rate of 100 ccs/kg/hour by diffusion alone is only possible in a spherical animal of about 1 mm. diameter. This is one aspect of the decrease in surface/volume ratio with increasing size. The surface area for oxygen intake decreases but the distances to be traversed increase in larger organisms. The need for a system of transportation within the body capable of carrying large volumes of oxygen from the respiratory organs to the tissues is clear. The physical process involved is basically one of convection.

(a) THE TRANSPORT OF OXYGEN

In many animals, including very nearly all vertebrates, transport of O_2 is assisted by the presence of a respiratory pigment in the blood. Among vertebrates this is haemoglobin which is contained within the red blood corpuscles. The effect of packing such large molecules into corpuscles is to decrease the viscosity of the blood to a level below that which it would be if all the haemoglobin were in solution. Mammalian red blood cells are non-nucleated and, except in camels, circular and bi-concave. The absence of nuclei increases the space for haemoglobin but probably decreases the life of the corpuscle. Most other vertebrates have nucleated, elliptical, bi-convex corpuscles which are generally larger than the non-nucleated ones of mammals. Red blood corpuscles of mammals are small, e.g.

8μ diameter in man, whereas the axes of the elliptical amphibian corpuscle may be as large as 25μ and 15μ (*Rana*), 53μ and 28μ (*Necturus*). The corpuscles of fishes range between $20\mu \times 14\mu$ (dogfish) and $10\mu \times 7\mu$ (white perch). In reptiles and birds the size range is approximately the same, those of birds being smaller than those of reptiles. The smallness of the corpuscles determines the minimum diameter that is possible in the capillaries. The finer the capillaries the closer the oxygen-carrying corpuscles can come to the tissue cells.

The advantages of a respiratory pigment in the blood are common to all animals. The first of these is to increase the oxygen-carrying capacity of the blood. If blood were water, it could carry only about 0.2 ml. of oxygen and 3.0 ml. CO_2 in each hundred ml. Vertebrate bloods can carry between 5 and 30 ml. O_2 /100 ml. blood (Table 1). The importance of this increased capacity is clear and it has been estimated that if all the oxygen were carried in physical solution instead of in combination with haemoglobin, a man would need either 30 times the volume of blood or the blood would have to circulate 30 times more rapidly. The oxygen-carrying capacity is greater in mammals and birds than among cold-blooded vertebrates, but even within these groups there are marked variations. Diving mammals such as seals have the highest capacity, the lowest being found in those fish in the antarctic which do not possess any haemoglobin. Mountain-living mammals, e.g. the llama, have high oxygen capacities. The oxygen capacity of the blood from active fishes is higher than that of sluggish species and very high oxygen capacities have been recorded in some fish which resort to air breathing.

The haemoglobin functions by giving up oxygen where the tension is lowest and absorbing it at high tensions. The relationship between tension and percentage saturation of the blood is not a linear one, however, and this is important for it increases the usefulness of the pigment, as is apparent from the dissociation curves shown in fig. 27. The sigmoid shape of this curve ensures that over the effective working range the amount of oxygen given up for relatively small changes in tension is very

Fig. 27.

Oxygen dissociation curves of some vertebrate bloods. (a) Fish and dog bloods at different CO₂ tensions. The two tensions are approximately those found in the tissues and lung of a dog, so that the actual curve for the operation of haemoglobin in the body lies between them. (b) *Protopterus* showing only a slight Bohr shift. (c) Maternal and foetal haemoglobin of a sheep. The O₂ tensions in the umbilical vein and artery, uterine vein and artery are indicated. (d) Shows the way in which fish bloods from deep water species (e.g., black-grouper) does not become 100% saturated in the presence of CO₂ even at very high pressures. In other species (long-nosed eel, full lines) the blood is fully saturated at the depths where the animal lives (indicated by blocks), even in the presence of high CO₂ tensions. (b, after Fish, G. R.: *J. exp. Biol.* Vol 33, 1956; c, after Barron, D. H. and Meschia, G., *Cold Spr. Harbor Symp.* Vol. 19, 1954; d, after Scholander, P. F. and van Dam, L. *Biol. Bull.* Vol. 197, 1954.)

great. The steep part of the curve usually coincides with the normal working range in the animal. Some indication of the position of the curves is given by reference to the *unloading tension* (T_U) i.e., the tension of oxygen at which the haemoglobin is 50 per cent saturated, and the *loading tension* (T_L) which is the oxygen tension at which it becomes 95 per cent saturated. It is in the interests of the animal that the unloading tension should be high, as this roughly defines the upper limit of the tissue oxygen tension. The loading tension must be related to the normal environmental oxygen tension, for if the latter never reaches the level required for full saturation, then clearly the haemoglobin will function inefficiently. In most cases there is a distinct 'safety factor', because the loading tension is usually less than the normal lower limit of the environmental oxygen tensions. Consequently there are some fairly definite correlations between T_L , T_U , and the environmental oxygen tension. Those amphibians and turtles which spend much of their time on land have their dissociation curves to the right of those for aquatic species. Fish which live in regions of high oxygen have their curves shifted to the right relative to those which inhabit stagnant waters. Mammals which live at high altitudes have lower values for T_U and T_L .

The haemoglobins of different species vary not only from one to another but also during the life cycle. A particularly notable example is found among mammals, where the dissociation curve for the foetal haemoglobin is quite distinct from that of the maternal haemoglobin. The curves for sheep blood, for example, lie to the left of the adult, i.e. the foetal haemoglobin becomes oxygenated at much lower pressures (fig. 27c). Similar differences between foetus and mother are found in snakes and fishes which have viviparous habits. These make it possible for oxygen to be transferred by diffusion from one system to the other. As in the fish gill, the exchange is aided by the counter-flow of the two media in the placenta. In viviparous animals, therefore, oxygen is transferred from air to maternal blood to foetal blood and finally to foetal tissue.

A further feature of haemoglobins which assists considerably

in the transport of oxygen from the respiratory organ and its liberation at the tissues where the oxygen tensions are low is due to the effect of pH and CO_2 content on the form of the dissociation curve. Fig. 27a shows this difference for the bloods of a fish and a dog. The effect of an increase in CO_2 concentration is to shift the curves to the right—the so-called '*Bohr shift*'. This has the important effect of increasing the amount of oxygen liberated from the haemoglobin in tissues where the carbon dioxide content is high. The curve indicating the dissociation of the blood pigment in the body between the lung and tissues is intermediate between the two curves shown in fig. 27a. It is apparent that there is an increase in the steepness of the curve over the effective range which produces a greater liberation of oxygen for a given difference in ambient oxygen tension. The Bohr shift is present in most forms having haemoglobin or haemocyanin as a respiratory pigment and in nearly all cases the blood eventually becomes 100% saturated at the higher oxygen tensions. In fish bloods, however, the effects of CO_2 or pH are very much more marked than in any other animals. They may be so great that the blood does not become 100% saturated even at greatly increased oxygen tensions. In some deep-water fishes it has been shown that a partial pressure of oxygen greater than 140 atmospheres may be required to saturate fully the blood with oxygen. This effect, that the blood does not become 100% saturated except at extremely high oxygen pressures, is known as the *Root effect*. It may have an important function in the liberation of oxygen in the swimbladder of many teleost fishes. Thus an increase in CO_2 concentration within the gas gland (p. 33) will lead to the liberation of O_2 . Such a mechanism cannot be involved in fish like the long-nosed eel because the pressures at the depths they inhabit (fig. 27d) are so great that their haemoglobin remains 100% saturated even at high CO_2 tensions ($\equiv$ pH 6).

In contrast to the fishes living in water of high oxygen content, those which occupy swamps and other regions of high CO_2 tensions have haemoglobins which are relatively insensitive to the CO_2 (fig. 27b). Most of these forms, e.g. the electric eel, have

adopted accessory air breathing and in consequence the CO_2 tension at the respiratory epithelium will be higher than in aquatic breathing. This decrease in sensitivity of the haemoglobin to CO_2 tension must have been a necessary physiological adaptation which preceded the adoption of the land habit. A similar decrease in sensitivity to CO_2 occurs in the respiratory centres of air breathers.

(b) TRANSPORT OF CARBON DIOXIDE

Blood pigments serve additional functions to those of oxygen transfer for they are important in the transport of carbon dioxide, both directly and as buffers, and in some instances they serve to maintain the colloid osmotic pressure of the blood. The amount of CO_2 dissolved in the blood far exceeds that which results from ordinary physical solution which would be no more than 2.5 vols. %. Arterial blood contains 45–50% and venous blood 55–60 vols. % CO_2 . Only about 10 vols. % are therefore given off in the lungs. Although most carbon dioxide is carried as sodium bicarbonate, about one-third of the total transported and liberated is in the form of HHbCO_2 , in which the CO_2 is directly combined with amino groups of the haemoglobin molecules. This *carbamino* compound reacts reversibly with oxygen, so that CO_2 is liberated when oxygen is taken up. This may take place rapidly and without any marked change in pH. When the CO_2 from tissue cells has diffused into the blood it dissolves by a slow reaction and form HCO_3^- ions. Some of the CO_2 diffuses into the red blood cells and there forms H_2CO_3 by a rapid process catalysed by the enzyme *carbonic anhydrase*. This carbonic acid subsequently dissociates into bicarbonate and hydrogen ions. The latter are buffered extremely efficiently by the haemoglobin. Thus if a quarter million molecules of CO_2 are introduced into the blood only one hydrogen ion remains. The increased production of hydrogen ions encourages the dissociation of oxyhaemoglobin to reduced haemoglobin and oxygen, which is given up to the cells. Most of the bicarbonate ions diffuse out of the red blood cells into the plasma and prevent the accumulation of an excess

Fig. 28.

Diagrams to illustrate the role of the red blood corpuscles in the transport of oxygen and carbon dioxide. (a) in the lungs, (b) in the tissues.

of positive ions in the corpuscle, and there is an inward movement of chloride ions. This is the only way equilibrium can be established because the red blood cell membrane is relatively impermeable to positive ions. This exchange is called the 'chloride shift' and serves the useful purpose of allowing a great deal of bicarbonate to be carried in the plasma.

In the lungs the haemoglobin takes up oxygen and the proportion of oxyhaemoglobin within the corpuscle is increased.

Oxyhaemoglobin is a stronger acid than reduced haemoglobin and consequently the equilibrium of the reactions is displaced with the result that CO_2 is liberated from the carbonic acid (fig. 28). It is clear, therefore, that the transport of oxygen and of CO_2 are complementary and provide an extremely efficient mechanism, not only for the uptake of oxygen and liberation of CO_2 in the respiratory organ but also for the liberation of oxygen in proportion to its requirement by the tissues. Furthermore, the presence of bicarbonate within the blood provides the so-called *alkali reserve* of the body. This is because bicarbonate forms a defence for the body against the production of excess acid. It is not the only alkali reserve in the body, for the proteins can neutralise considerable amounts of acid. Considered as a physico-chemical system the ratio of bicarbonate ions to free CO_2 is only about 1/20, which is a poor buffer-ratio. Nevertheless, because the nervous regulation is tuned to maintain a constant pH and CO_2 content of the blood this physiological or heterogeneous buffer action transforms the carbonic acid-bicarbonate system from a rather poor buffer into a very good one. The lungs, of course, provide a path by which a great excess of acid in the form of CO_2 is removed from the body. In this system, which is vital for the maintenance of the acid-base balance of the body, the corpuscles are most important in the formation of bicarbonate and the plasma is best for its storage.

The function of blood pigments in raising the colloid osmotic pressure of the blood is absent from vertebrates because the pigment is contained within the corpuscles. As we have seen, this adaptation reduces the viscosity of the blood and yet preserves its high oxygen-carrying capacity.

The Heart and Circulatory System in Relation to Aquatic and Aerial Respiration

It is already clear that the structure and function of the cardio-vascular system are very closely linked to the respiratory mechanisms of an animal. Nowhere is this so clearly shown as in the structure of the heart and aortic arches of vertebrates, which show progressive modifications as we ascend the series from fish to mammal. Many aspects of the physiology of the lower vertebrates remain to be investigated, but sufficient is known to suggest that these structural changes are associated with modifications in function which lead to a more efficient supply of oxygen to the tissues. The general course of evolution has been from a gill-breathing form with a single circulation to the birds and mammals with their efficient lungs and double circulations. The variety of types of heart and circulation which has persisted in living forms gives us a few glimpses of the way in which this functional system has changed during vertebrate evolution. Coupled with the changes in the heart and aortic arches will have gone changes in the respiratory mechanisms and the nervous control of both the cardio-vascular and respiratory system.

The primitive chordate circulatory system consisted of a ventral heart behind the branchial region which led anteriorly into the ventral aorta. Passing round the pharynx from the ventral aorta were a number of vessels which, after forming a capillary network in the gills, joined a lateral dorsal aorta on each side and these led posteriorly into the median dorsal aorta running backwards along the whole length of the animal. The organs of the body were supplied with blood from this main vessel and after passage through the capillaries the blood

returned to the heart in the venous system. This *single circulation* had a pump, a respiratory capillary system, and a tissue capillary system all *in series* with one another. This type of circulation is found in the majority of gill-breathing systems. The precise way in which the capillary network of the gills develops from the embryonic aortic arch varies from group to group (e.g. the original embryonic arch mainly forms the afferent vessel of selachians but gives rise to the single efferent vessel in teleosts). Nevertheless, six aortic arches are found in nearly all modern fishes, at least during development, and this is also true of higher vertebrates.

(a) *The heart and aortic arches in fishes*

The fish heart consists of four or five chambers in series with one another. These are the sinus venosus, the auricle, the ventricle, the conus arteriosus, and bulbus arteriosus. They are usually bent in an S-shape as, for example, in the heart of a dog-fish (fig. 29b). As with most elasmobranchs the heart in its pericardial cavity is enclosed in the cartilaginous case formed by the skeleton of the pectoral girdle. The pericardial cavity communicates with the perivisceral coelom through a fine canal (*pericardio-peritoneal canal*) in which there are valves which allow fluid to escape from the pericardium but prevent the entry of fluid in the opposite direction. There is no bulbus in cartilaginous fishes and blood is forced forwards to the ventral aorta when the ventricle and conus contract. It is then forced up the afferent branchial vessels (fig. 30a) where the pressure varies between 15 and 21 mm. Hg at different phases of the cardiac cycle. The pressure in the efferent branchial vessels and dorsal aorta is less, and the size of the pulse pressure is also reduced because of the resistance of the branchial capillaries (fig. 29a). The blood subsequently circulates through the capillaries in the body musculature and viscera before its return to the heart through the large sinuses which offer little resistance to flow. The pressure in the venous sinuses is extremely small and the problem of how the circulation is completed is a real one. The effect of the position of the heart in a rigid box is of importance

Fig. 29.

(a) Pressures in different parts of the dogfish circulatory system. Actual wave-forms are given from the afferent branchial and coeliac arteries (after Satchell, G. H.: *J. exp. Biol.* Vol. 37, 1960). The corresponding pressures that probably take place in the sinus venosus are shown by dotted lines. (b) L.S. through a dogfish heart.

in this connection, for it ensures that constant volume must be maintained within the pericardial cavity. Hence when the ventricle contracts there will be a tendency for the volume of the pericardial cavity to be reduced and this can only be maintained at its original size if blood flows into the auricle from the sinuses and sinus venosus. Consequently there will be a reduced pressure within the sinus venosus which will be opposite in phase to the increased pressure in the ventral aorta. This mechanism of filling the heart is described as an *aspiratory pump*. During its passage through the other chambers of the heart there is a gradual build-up in the blood pressure until it reaches its highest value in the ventral aorta. Each of the junctions between sinus venosus and auricle, auricle and ventricle, is guarded by valves which prevent any reversal of flow when these chambers contract. There are

also rows of semi-lunar valves in the conus which perform a similar function between the ventral aorta and the ventricle.

The circulation of teleosts is fundamentally the same as that described for a cartilaginous fish but here the conus has been lost and is only represented by these semi-lunar valves at the base of the *bulbus arteriosus*. This latter swelling of the base of the aorta is non-contractile, and functions to even out the pressure wave of ventricular systole.* The teleost heart is not usually surrounded by a rigid pericardial box although its walls will tend to maintain a constant volume and thus the heart may still have some aspiratory action assisting the venous return. The veins are much smaller in cross-sectional area and this, together with other modifications of the detailed

Fig. 30.

Diagrams of the arterial arches of (a) *Squalus acanthias* (a dogfish), (b) *Scaphirhynchus* (a sturgeon), (c) *Neoceratodus*, (d) *Lepidosiren*. The coronary circulations (cor.) are as indicated: hy.a. = hyoidean artery; d.a. = dorsal aorta; sub.c. = subclavian artery; pul. = pulmonary artery (various authors, from Foxon, 1955).

* 'Systole' is the phase when a heart chamber contracts whereas 'diastole' is when it is relaxing.

plumbing in the branchial circulation (fig. 30b), have the result that the blood volume is only one-third that of a typical selachian. Furthermore, the pressures recorded in the ventral and dorsal aorta are much greater, e.g., in the salmon, the ventral aorta pressure is 75 mm. Hg. and 53 mm. Hg. in the dorsal aorta. These modifications result in a faster circulation time than is probable in the dogfish, but where they have been measured, as in the eel, circulation is still slow (20–120 seconds) as compared with man (30 seconds including the pulmonary circulation). There are no valves in the veins of fishes but no doubt muscular movements do play a part in maintaining the venous return.

(b) *Circulation in bony fishes with air-breathing organs*

Many fishes living in conditions unfavourable for branchial respiration have evolved organs where oxygen may be absorbed from air obtained by gulping from above the water surface. As explained in Chapter 3, these organs are usually modified regions of the alimentary canal and receive their blood supply in a manner typical for their region of the gut. The blood supply to some of these organs is given in Table 4, where a division is made into those which return blood into the general body circulation and those in which the return is direct to the heart. Before considering the latter in some detail, it is of interest to notice that some fishes have the circulation to the accessory breathing organs *in parallel* with the gill circulation (e.g., the African and Indian catfishes *Clarias* and *Saccobranthus*) so that the oxygenated blood which leaves the organ is distributed to all the rest of the body. This contrasts with most other species where the accessory circulation is *in series* with the gill circulation and hence it only serves to boost the oxygen tension in the general circulation. It is thus theoretically possible to have a single circulation in which the gills are replaced by an air-breathing organ, which might well have been a lung. In fact, of course, the evolution of lung-breathing in tetrapods is associated intimately with the evolution of a double circulation, which makes it possible for the blood pressure to be raised before the oxygenated blood is circulated to the main organs of the body. It is

because of this that the condition of the heart and the circulation to the lung of the Dipnoi (lungfishes) is of especial interest.

(c) *The heart and aortic arches of Dipnoi*

In all three living genera the auricle is divided completely, the left one receives blood direct from the lungs in the pulmonary veins. The presence of oxygenated blood on the left side of the heart is general throughout all tetrapods. The two auricles communicate with the ventricles by apertures which are protected by 'valves' which are not homologous with the auriculo-ventricular valves of other vertebrates (see p. 112). The ventricle is almost completely divided and the separation of oxygenated and de-oxygenated blood is maintained throughout the conus by a complex and twisted valve. This valve develops from four longitudinal ridges and more or less completely divides the conus into two sections. During its passage up the conus, the blood rotates in a clockwise direction through 270° . Hence blood from the right auricle comes to lie in the dorsal section of the conus at the base of the ventral aorta and blood from the left auricle occupies the ventral section. In *Lepidosiren* these two parts of the ventral aorta are joined respectively to the 5th and 6th arches and the 3rd and 4th arches (fig. 30d). Thus de-oxygenated blood from the right auricle is directed to the 5th and 6th arches which supply the lungs. The oxygenated blood from the left auricle passes anteriorly in the ventral part of the aorta to be distributed in the 3rd and 4th aortic arches, to the head and general body circulation. The degree of separation maintained in the conus between these two lots of blood is not so great in *Protopterus* and is least in *Neoceratodus*, which is said to be unable to breathe air for any length of time.

It is of interest to notice that the heart itself receives a special blood supply which, in *Lepidosiren*, is derived from the 4th aortic arch which may therefore be presumed to contain oxygenated blood. The hearts of the majority of fishes contain only de-oxygenated blood and hence the need for a supply of oxygenated blood is particularly important. In most of them it is derived from a special hyoidean circulation which has its origin

from one of the *efferent* branchial vessels. A subsidiary coronary circulation is also derived in many cases directly from the dorsal aorta.

(d) *The heart and aortic arches of Amphibia*

At first sight the presence of a single undivided ventricle in the heart of most Amphibia seems to provide an ideal intermediate stage between the single circulation of a fish and the circulation of reptiles where the ventricle is partially divided. Suggestions about the way in which different types of blood can retain their separateness within the undivided ventricle have been discussed many times and have renewed their interest with the application of more modern techniques to this problem. The classical descriptions of the fate of the blood from the two auricles were based upon the absence of any mixing of the blood in the ventricle, together with the passage of the different bloods consecutively into the conus which arises from the right side of the ventricle. Initially blood from the right auricle was considered to pass up the conus (here often called truncus) and into the pulmo-cutaneous arch (6th aortic arch) because of its low peripheral resistance. Later the remainder of the right auricle blood, together with some oxygenated blood from the left auricle, would pass up the truncus to be distributed in the systemic (4th aortic arch), and finally pure oxygenated blood would be forced into the carotid arch (3rd aortic arch). Since Brücke and Sabatier proposed this mechanism, several workers have doubted various parts of it. For instance, injection of dyes into the venous return to the heart gave evidence for a random distribution of the left and right auricular bloods into the three arches, and pressure measurements in the arches themselves suggested a simultaneity of the pulse pressures. X-ray-opaque material has recently been used to follow the distribution of blood into the aortic arches, and Foxon observed a random distribution following its injection into the pulmonary vein. These results led to some scepticism concerning the classical hypothesis and a greater appreciation of the mixing hypothesis (fig. 31). Foxon observed, however, that the two sets of blood did not mix completely in the ventricle,

which supported part of the classical hypothesis. Most recent researches into this problem have confirmed the latter observation. If *large* quantities of dye are injected, however, the blood appears to show mixing of the streams not only in the ventricle but also in their passage up the conus. Ideally, no more than 0.001 ml. of dye (Evans blue is frequently used) should be injected. In the frog and toad it has been observed that blood from the right and left auricles maintains its separateness during its passage up the conus although both streams enter the conus simultaneously (fig. 32). This separation is largely because of the presence of the spiral valve in these forms. Furthermore, recordings of changes in the blood pressure throughout the cardiac cycle using modern techniques have confirmed completely that the pulse waves are simultaneous in all three arches in *Rana*, *Bufo*, and *Xenopus*. During their passage up the conus the streams of blood pass into different aortic arches because

Fig. 31.

The supposed path of the blood through the heart of the frog according to A. The classical hypothesis, B. The mixing hypothesis c.a. carotid arch; l.a. left auricle; p.c. opening of conus arteriosus to pulmo-cutaneous arch; p.c.a. pulmo-cutaneous arch; r.a. right auricle; s.a. systemic arch; s.v. spiral valve; v. ventricle. (from Foxon, 1955.)

of the morphological relationships of these streams and the exits of the arches at the anterior end of the conus. The precise nature of the separation achieved by these mechanisms varies in the species that have been examined so far. For example, in *Xenopus*

Fig. 32.

The path of the blood in the conus of *Rana* as indicated by the injection of very small quantities of Evans blue. (b) Superimposed pressures recorded from two arches in a toad (modified after Simons, 1959.)

the right auricle blood only goes to the pulmo-cutaneous arch whereas in *Rana* and *Bufo* it mainly goes by this route but some also enters the left systemic arch. Furthermore, blood from the left auricle enters all three arches in *Xenopus*, but in

Rana and *Bufo* it is distributed mainly to the carotid and right systemic and never goes to the pulmo-cutaneous arch. These variations among the Anura are quite probably associated with differences in their respiratory mechanisms. For example, *Xenopus* is known to depend more on cutaneous respiration than the other two genera and associated with this it has been found that over a half of the total ventricular output passes into the pulmo-cutaneous circulation and especially that part which goes to the skin. In urodeles, where cutaneous respiration is also of great importance, there is far less separation of the blood from the left and right auricles in the conus largely because of the absence of a spiral valve. The probable mechanism of this valve in *Rana* and *Bufo* is illustrated diagrammatically in fig. 32, where it is suggested that the blood from the ventricle makes a clockwise spiral even before it enters the base of the conus. This has been observed from ciné-injection experiments and it is also present in forms without a spiral valve. It seems to be a property of the hydrodynamics and the contractile mechanism of the ventricle in these forms. Measurements of the oxygen tension or the relative volumes passing into the different arches have not been made in *Rana* or *Bufo*. Until these are available it must be realised that the terms oxygenated and de-oxygenated blood, although convenient, may be misleading. In the urodele, *Amphiuma*, it has recently been shown that the blood in the systemic arch is richer in oxygen than that in the pulmo-cutaneous arch, but this difference is reduced at low blood pressures.

During metamorphosis the tadpole passes from a fish-type circulation to that of the adult. At one stage it has external gills which are replaced by internal gills. Various parts of the ancestral pattern of six aortic arches persist in Amphibia; for example, the *ductus caroticus*, which connects the third and fourth aortic arches, persists in Apoda (legless Amphibia) and in some adult urodeles such as *Triton*. The *ductus arteriosus* (ductus Botalli), which connects the pulmonary and systemic arches, is lost in adult Anura but is found in most Apoda and Urodela. The urodeles also show the presence of a persistent 5th aortic arch which is entirely lost in all other tetrapod adults.

Despite the convincing evidence which has now been brought forward to support the view that the blood from the right and left auricles is not distributed at random into the aortic arches, there seems little doubt that the separation achieved by the dipnoan heart is far greater. The complete absence of physiological work on the heart of the Dipnoi makes this a difficult comparison, however, because future investigations may well show that the separation, at least in *Protopterus* and *Neoceratodus*, is less than might be supposed on morphological evidence. Nevertheless, it must also be appreciated that the modern Amphibia have departed considerably from the habit and mode of life of their ancestors which were the progenitors of the main tetrapod stock. In attempting to deduce the type of heart and arterial circulation of the early land vertebrates it may be preferable to take the dipnoan heart with an almost completely divided ventricle as a model. On this view the single ventricle of modern amphibians represents a form in which the inter-ventricular septum of its crossopterygian ancestor has become reduced in relation to its more specialised respiratory habits, chiefly in the greater use of cutaneous respiration. On the other hand it must equally be remembered that the heart of modern dipnoans also shows specialisation in its structure indicative of a departure from the main line of evolution. The atrio-ventricular opening is guarded by a fibrous or partly cartilaginous plug which arises from the posterior margin of the opening. It is moved by muscles attached to the inter-auricular and inter-ventricular septa and is a structure peculiar to the Dipnoi.

(e) *The heart and aortic arches of modern reptiles*

The heart of all reptiles has two auricles and the ventricle is partially divided, but details of the inter-ventricular septum are complex and vary between different groups. The conus of all reptiles is divided from its origin at the ventricle into three sections, namely the pulmonary, right systemic, and left systemic arches. The division of the ventricle is complete in crocodiles but incomplete in all other groups. The lizard (*Lacerta*) heart (fig. 33) may be taken as an example which immediately

shows the complexity of these hearts, for *both* auricles open into a single ventricular chamber which corresponds to the left ventricle but is dorsal in position. The main septum is nearly horizontal and incomplete anteriorly. The larger dorsal chamber extends posteriorly and it is into this that the two auricles open and from which arise the two systemic arches. The dorsal chamber communicates with the smaller ventral chamber (cavum ventrale) via the edge of the incomplete septum and this is the route of all blood which enters the pulmonary arteries, as they arise from the ventral chamber. The course of the blood deduced from a morphological study of the aortic arches suggests that the

Fig. 33.

The heart of *Lacerta viridis*. (a) Ventral view showing the ventricle opened up and the path of the blood from the auricles to the different aortic arches. (b) Transverse section through the ventricle just behind the openings from the auricles. The relative positions of the auriculo-ventricular valves and of the origin of the three arches are shown as seen from behind and looking forwards to the anterior part of the ventricle. Oxygenated blood in full lines; deoxygenated blood in dotted lines.

pulmonary contains deoxygenated blood derived from the right auricle whereas the right systemic contains the most oxygenated blood and both carotid arches arise from this systemic artery. The left systemic would be expected to contain mixed blood, being intermediate both in the position of its origin at the ventricle and in the part of the body which it supplies.

X-ray cinematography of hearts following the injection of radio-opaque material into the veins near the heart has fully confirmed this account. There appears to be little mixing of the blood in the dorsal ventricular chamber and all blood entering the pulmonary arch is derived from the right auricle while the right systemic conveys blood entirely derived from the left auricle. The left systemic carries a mixture of blood from both sources. These studies also revealed that the path of the blood in the ductus caroticus, which persists on both sides, is from the systemic to the carotid arch. In this way the left internal carotid (fig. 33a) receives some mixed blood from the left systemic.

In the *Chelonia* (tortoises and turtles), both the pulmonary and left systemic arches arise from the right side (= cavum ventrale of lizard) of the ventricle, the right systemic arising from the left side of the ventricle as before. As in the lizard heart, both auricles open into the same ventricular chamber which corresponds to the left ventricle. When the auricles contract, blood from the right auricle passes rapidly across the incomplete septum and following ventricular systole it becomes distributed to the pulmonary and left systemic arches alone. Oxygenated blood from the left auricle is distributed in the right systemic arch. Accounts of turtle and lizard hearts based on measurements of O_2 tensions confirm that blood passing to the pulmonary arch contains much less oxygen than that in the systemics. It appears, however, that the blood in both the right and left systemic arteries has very nearly the same O_2 tension.

It is only in the crocodiles that one important condition for a double circulation is found. This is that the auricles open separately into two separate ventricles (fig. 34a). The left auricle opens into the left ventricle which communicates with the right systemic from which arise both carotid arches. The right auricle

pumps blood into the right ventricle which communicates with both the pulmonary and left systemic arches. A feature which is peculiar to the crocodile heart is found shortly after the two systemic arches have arisen from the two ventricles. In this region there is a small *foramen of Panizza*.

The differences between various extant reptiles are not surprising when it is remembered that they are derived from stocks which have been separate for a very long time. The crocodile heart is of particular interest because it is easy to derive that of

Fig. 34.

Ventral views of the hearts of (a) a crocodile, and (b) a bird.

birds from it. Thus from fig. 34 it is clear that closure of the foramen of Panizza, together with the loss of the left systemic, would lead to a complete double circulation which would be funda-

mentally the same as that found in birds. This relationship is supported by developmental studies which reveal that the ventricular septa in these two groups are homologous. Both these septa develop in a way which is completely different from the inter-ventricular septum of the Dipnoi, the horizontal septum of lizards and other reptiles, and the inter-ventricular septum of mammals.

Further evidence for the close relationships between crocodiles and birds which may be derived from the circulatory system is shown when the part of the carotid system which has become elongated in the neck is examined. In the crocodile and bird the elongation occurs mainly after the third arch has passed round to the dorsal side whereas in the lizards and snakes the elongation occurs ventrally. The inter-ventricular septa of crocodiles and birds are in fact homologous with the dorsal ridge of the lizard ventricle (fig. 33b). All these features are to be expected from the palaeontological evidence which shows conclusively that birds and crocodiles are both derived from the ruling reptiles or Archosauria whereas the lizards and snakes arose from a different stock, the Lepidosauria.

The persistence in many modern reptiles of the left systemic arch, ductus arteriosus, and ductus caroticus, together with an incomplete inter-ventricular septum in all except crocodiles, provides many possibilities for the inter-mingling of streams of blood which are separate in birds and mammals. The presence of these short-circuits (fig. 35), especially between the pulmonary and systemic circulations, is indicative of some 'inefficiency' in the mechanism as a whole. If, as seems probable, the inter-ventricular septum was almost complete in the earliest Amphibia or Crossopterygii, then such an incomplete separation must have persisted for a long time. The possibility that it may have some definite functional significance has been considered many times but no fully satisfactory reason has been given for its presence, largely because details of the volumes circulating in different parts of the vascular system are unknown for any reptile. One reasonable suggestion, however, is that these persistent portions of the ancestral system represent 'shunts' which make

Fig. 35.

Diagram of the circulation in reptiles, birds and mammals to illustrate the different places where blood can be short-circuited between the systemic and pulmonary circulations. These 'shunts' are respectively: (1) The foramen ovale, (2) an incomplete inter-ventricular septum, (3) foramen of Panizza, (4) the right systemic of reptiles, (5) the ductus arteriosus.

it possible for any excess blood in one part of the system to pass across into another portion where the pressure is not so great. With reference to the systemic and pulmonary circulation, this would clearly have advantages in early tetrapods where the lungs are relatively undeveloped and their capillary bed quite likely to be unable to take sufficiently large volumes of blood. On this view it is supposed that only when the lung had evolved sufficiently did it become possible for the pulmonary circulation to take the same amount of blood as the systemic circulation. For it is a condition of a complete double circulation that both circuits should be able to carry equal volumes of blood in unit time. If these persisting portions of the system do function as 'shunts', they play an important role in the functioning of the reptilian cardio-vascular system. Unfortunately, details of their working are not available and this supposition remains unproven. The few blood pressure recordings that have been made on reptile hearts suggest, however, that the resistance to flow through the lung is not as great as has been generally supposed.

An alternative hypothesis which also entails their function as shunts between the pulmonary and systemic circuits is suggested by the recent work on *Xenopus* and more especially by analogy with the circulation of the mammalian foetus at birth. This latter system has been worked out in great detail and is discussed below. In both the adult *Xenopus* and the mammal shortly after birth, it appears that, despite the relative inefficiency of the lung, the volume of blood passing through the pulmonary capillaries *exceeds* the volume passing round the rest of the body. In this way compensation is made for the relative inefficiency of the respiratory organ at taking up oxygen. In the young mammal blood is shunted from the systemic circuit through the ductus arteriosus and into the pulmonary circulation, rather than the reverse which might be expected and is the case before birth. There appear to be no observations on the path of the blood through the ductus arteriosus of reptiles nor is there any information available about the relative volumes of blood flowing round the pulmonary and systemic circuits. It would be a possible solution to their respiratory problems if a greater volume of blood passed to the lung in order to compensate for the relative inefficiency of their gaseous exchange. On this view the evolution of a respiratory organ capable of an efficient gaseous exchange is stressed rather than the change in the pulmonary capillary resistance involved in this changed lung structure. Of course it is very probable that both a decrease in resistance to blood flow and an increase in its efficiency for gaseous exchange would have gone hand in hand.

(f) *The mammalian double circulation*

It is apparent from the considerations given above that the mammalian circulation cannot be derived from any known reptilian type, for completion of the inter-ventricular septum would lead to a pair of very unequal ventricles as one would receive blood from both auricles whereas the other would become a closed chamber. A further difficulty is that in all modern reptiles both carotid arches arise from the right systemic whereas in all mammals they take their origin from the

left systemic. These difficulties are due, of course, to the fact that among modern reptiles there are only representatives of the diapsid line of evolution which was distinct from that which gave rise to the mammals. It seems, therefore, that in attempting to look for a common ancestral pattern from which to derive the mammalian circulation we must look at something like the dipnoan type of heart and aortic arches. From such a beginning, it is probable that the first stage in evolution was the separation of the pulmonary arch from the rest of the conus; such a primitive type could lead directly to the mammalian system via reptiles in which the carotids came off the *left* systemic arch. Unfortunately, there are no living descendants of the synapsid line of reptiles which gave rise to the mammals and it is for this reason that such a large gap exists in our comparative morphological story. One important feature which both birds and mammals have in common, however, is that the systemic arch which persists in both groups is that which takes its origin from the left side of the ventricle. This is of fundamental importance because in all vertebrates where the oxygenated and deoxygenated bloods are separated, the *left* side of the heart receives the blood which is returned from the lung.

(g) Structural and physiological changes in the mammalian heart and circulation at birth

All six embryonic arches are represented during the development of mammals, but not all appear at the same time. Those persisting in the adult are the 3rd, 4th, and 6th arches which, as in other tetrapods, respectively become the carotid, systemic, and pulmonary arteries. In the development of the venous system, a similar recapitulatory series is present, for the posterior cardinal veins appear early and later give way to the inferior vena cava which has complex homologies.

It is, however, in the later stages of development just prior and immediately following birth that the most interesting features are found. The circulation of a foetal lamb is shown diagrammatically in fig. 36. The four-chambered heart functions as two parallel pumps which serve to circulate the whole foetus, as was

pointed out in 1628 by William Harvey. The two circuits are not separate, and blood enters both auricles from the inferior vena cava because the *foramen ovale* remains open until just after birth. The lungs only receive about 10% of the combined ventricular output. Extra blood pumped out of the right ventricle is shunted into the systemic circuit via the functional *ductus arteriosus*. The foetal blood is oxygenated at the placenta and passes through the liver in the umbilical vein to become mixed with deoxygenated blood returning from the rest of the tissues in the inferior vena cava. 60% of this blood is deflected into the left auricle through the *foramen ovale*. The remaining 40% enters the right auricle and becomes mixed with deoxygenated blood returned in the superior venae cavae and is pumped to the right ventricle. Blood from the left side of the heart is forced out of the aorta and some passes into the brachio-cephalic artery supplying the head and anterior limbs but most flows into the descending aorta.

In fig. 36 the percentage saturation of the blood with oxygen is indicated for different parts of the circulation. These figures were determined within a short period (5–15 seconds) of one another and from them it is possible to deduce the proportions in which any two blood streams become mixed with one another. For example, the right auricle receives blood returning in the inferior vena cava (67% saturation), and from the superior vena cava (31% saturation). After being pumped into the right ventricle this blood passes into the pulmonary artery where the blood is 52% saturated. Hence it follows that the proportion of inferior vena cava to superior vena cava blood in the right auricle is approximately 2:1. Similarly, on the left side of the heart blood from the inferior vena cava and pulmonary vein becomes mixed in the proportion of about 4.5:1. It can also be calculated that 40% of the total ventricular output passes along the *ductus arteriosus* from the pulmonary artery to the main systemic aorta. In this way a very complete picture of the circulation in the foetus has been developed as have the changes following severance of the umbilical cord, some of which are summarised below.

When the cord is tied the source of oxygenation is cut off and this results in a fall of the oxygen tension in the circulating blood. This leads to stimulation of the respiratory centre in the medulla and the lungs become filled with air. A further result of cutting off the placenta is to decrease the volume of blood

Fig. 36.

A diagram to show the main parts of the circulatory system in a foetal lamb. The percentage saturation of the blood with oxygen is shown for different parts of the circulation. The size of the vessels indicates the relative volumes of blood flow. (Data of Born, Dawes Mott and Widdicombe, 1954.)

returning to the right side of the heart. Contrasting with this, there is an increase in the volume of blood returning to the left auricle because expansion of the lungs leads to a decrease in the resistance to flow of blood in the pulmonary circuit. This differ-

ence in the relative volumes of blood returning to the two auricles operates across the inter-auricular septum and causes the foramen ovale to close. Its structure is such that it functions as a valve allowing blood through to the left auricle but it closes when the pressure on the left side is the greater. Differential growth normally results in the complete healing up of this aperture in the adult mammal. If it does not heal up the mammal is said to have 'a hole in the heart' which leads to the condition known as 'blue baby' which nowadays can successfully be cured by cardiac surgery. A further significant effect of cutting the umbilical vein and artery is to reverse the direction of blood flow in the ductus arteriosus which can be heard as a 'murmur' because of the turbulence set up in the flow through this duct as it narrows. The reversed flow is the effect of a decrease in resistance of the pulmonary circuit and an increase in resistance of the systemic circuit due to the removal of the placental circulation. Consequently, the pressure in the systemic circuit exceeds that in the pulmonary and blood flows in the reverse direction from systemic to pulmonary artery through the ductus arteriosus.

All the changes described above occur *within minutes* of the delivery of a lamb and result in the establishment of the so-called *neonatal* circulation (fig. 37). This is exactly the same as the adult circulation with the exception of an open or patent ductus arteriosus which shunts blood from the systemic to the pulmonary circuit. It has been suggested that this circulation is of great adaptive value in the early stages of mammalian existence because it counteracts the disadvantages of the inefficient gaseous exchange occurring in the lungs at this time. Thus one result of a fall in oxygen tension of the blood is by reflex action to raise the blood pressure. The flow of blood from the systemic to pulmonary circuit will therefore increase and the volume of blood passing to the lungs will be augmented so that it exceeds the volume circulating to the rest of the body. The importance of the patent ductus arteriosus at this time is emphasised by the marked lowering of the oxygen saturation of the blood if it is experimentally occluded. Under these conditions the percentage

saturation of the blood in the carotid artery is lowered by 10–20%, which indicates to what extent the patency of the ductus arteriosus compensates for the relative inefficiency of the respiratory exchange. Occlusion of the ductus arteriosus normally takes place by differential growth and its constriction is complete within a day of birth, but it already begins one-quarter of an hour after the delivery of the new-born lamb. In other mammals its complete occlusion may take a much longer period,

Fig. 37.

Diagrams of the changes in circulation which occur at birth of a lamb (from Born, Dawes, Mott, and Widdicombe, 1954).

notably some aquatic mammals such as seals and whales where it may be patent for as long as 20 days after birth.

The knowledge obtained about this circulation during the change from an incomplete to a complete double circulation

reveals the many factors which are involved in the functioning of such systems with incomplete separation of the oxygenated and deoxygenated bloods. The vital importance of the shunts between the two main circuits is easily appreciated. Before birth both the foramen ovale and the ductus arteriosus perform vital functions as does the ductus following the tying of the placenta. One interesting feature is the evidence that the inefficient functioning of the lungs is overcome by an increase in the flow of blood in the pulmonary circuit. As has been mentioned earlier it is usually assumed, when discussing incomplete circulations of lower vertebrates, that the lung capillaries are unable to take a sufficient volume of blood to enable the separation of the two circuits to have evolved. It now seems probable that under these conditions the shunts in the circulation function by allowing more blood to pass to the lungs from the systemic circuit, especially during increased activity of the animal.

Cellular Respiration

We have traced some of the many adaptations found among vertebrates for extracting oxygen from their environment and transporting it in the circulatory system to their tissues. Adaptations have also been described which exist for the removal of carbon dioxide derived from metabolic activities within the cells. The nature of these cellular processes and some aspects of the overall performance of the respiratory mechanism will now be discussed.

Some indication of the total performance is gained from determinations of the volumes of these two gases.

The ratio $\frac{\text{volume of CO}_2 \text{ given out}}{\text{volume of O}_2 \text{ absorbed}}$ is called the respiratory quotient (RQ). The overall reaction for the combustion of a carbohydrate such as glucose is given below:

From this equation it can be calculated that 1 gram of glucose reacts with 0.75 litres of oxygen to form an equal volume of CO_2 . The RQ when carbohydrates are used as the respiratory substrate is therefore approximately 1. For fats the $\text{RQ} = 0.7\text{--}0.71$ and for proteins $0.80\text{--}0.82$. As a general guide to the type of respiratory substrate being used these figures have a certain value, but they cannot be relied upon invariably. The relative volumes of O_2 and CO_2 exchanged at the respiratory organ may be affected by many factors, such as acidosis, hyperventilation, and other respiratory irregularities. Inter-conversion of foodstuffs, and other metabolic activities may also affect the RQ.

The precise mechanisms whereby the oxygen is utilised by the organism and the CO_2 evolved and, what is more important, how energy is made available by the degradation of the large molecules of the animal, are beyond the scope of this book. Nevertheless, it seems inappropriate to leave the oxygen just at the point where its most significant effects are to take place. The parts of the cellular mechanisms which use molecular oxygen will first be discussed before going on to consider the energy-releasing processes. In some ways this is a reversal of the normal view presented by biochemists, who usually begin with the large molecules and discuss their progressive degradation and later consider oxidation of the end products by molecular oxygen. Equally of course, many important processes of cellular respiration can take place in the complete absence of oxygen, and is the rule in some organisms. Anaerobic respiration provides far less energy, however, and is certainly not the normal mechanism found among vertebrates. Following a period of exercise extra O_2 is taken up in order to complete the breakdown of respiratory substrates, but some fishes (e.g. carp) do not show this after periods when their O_2 supply has been reduced to almost zero.

(a) THE CYTOCHROME SYSTEM

In all aerobic respiration the molecular oxygen functions as the final agent which takes part in the removal of hydrogen from a substrate which is therefore oxidised. In fact it is mainly concerned to oxidise one particular substance, namely *cytochrome*. This is one of a series of chromo-proteins which are very similar in structure to haemoglobin, for they are made up of a haem-prosthetic group and protein portions with molecular weights of about 13,000. The vital importance of the cytochrome system, rediscovered and named by D. Keilin, is indicated by the profound effect of hydrogen cyanide on nearly all living organisms. This poisons the cytochrome system and stops between 80 and 90% of aerobic respiration. It may be concluded therefore that at least this proportion of the oxygen which enters the blood stream of vertebrates is utilised in the tissues by this route. The

action of the cytochrome system may be indicated in the diagrams below which show how a substrate to be oxidised (AH_2) reduces the cytochrome and is itself oxidised in the presence of a specific dehydrogenase enzyme.

The reduced cytochrome so produced has its iron in the ferrous condition and it is oxidised to the ferric state by combination with molecular oxygen, the latter reaction being catalysed by another member (a_3) of the cytochrome system—*cytochrome oxidase*. This enzyme is the cyanide-sensitive component. Cytochrome therefore functions as an electron carrier which is able to pass on the hydrogen to molecular oxygen and is then restored to its original condition. In doing this the two hydrogen atoms attached to the AH_2 can be thought of as two protons and two electrons. The latter reduce the ferric cytochrome c to the ferrous condition, but this is immediately returned to the oxidised state because cytochrome oxidase takes the electrons and causes them to unite with the two protons and oxygen to form water. By this cyclical mechanism small amounts of the cytochrome system can participate in the oxidation of enormous amounts of materials in the cells.

The presence of cytochromes in the cells of many organisms has been demonstrated spectroscopically, for they have very characteristic absorption spectra when in the reduced form. The oxidation of reduced cytochrome can readily be demonstrated in suspensions of yeast. When oxygen is bubbled through such a suspension there is no absorption spectrum visible but when it is stopped and nitrogen bubbled through instead, the spectrum of the reduced cytochrome immediately shows itself. The re-admission of oxygen to the suspension immediately removes the reduced cytochrome. It is clear, therefore, that the yeast cells contain systems which are not only able to reduce cytochrome but also others whereby it can be reoxidised by molecular oxygen.

If we now enquire into the nature of the substrate AH_2 we find that usually it is not a simple organic degradation product of glucose, but a relatively complex molecule of the group of substances known as *flavoproteins*. These are also carriers which receive the hydrogen from earlier stages in the long sequence of coupled reactions which occur during the degradation of a single glucose molecule. The large number of these separate steps is one of the remarkable features of the biochemistry of cells.

(b) ENERGY RELATIONSHIPS

Even the system which we have summarised above for the mechanism of cytochrome c and cytochrome oxidase is a very much abbreviated form of the mechanisms now known. It is not unreasonable to ask, therefore, why such a complicated chain of

* DPN = diphosphopyridine nucleotide.

events should be required. From the equation given above it is apparent that burning a single molecule of glucose yields 690,000 calories of energy per gram-molecular weight (i.e. 180 grams glucose) in the form of heat. But the animal does not require such large amounts of heat for, unlike a steam engine, it does not have the machinery available for converting it into work. Furthermore, the liberation of such quantities of heat would have serious consequences on the body temperature! What the body requires is a system whereby this total chemically-bound energy is made available in a series of small packets, each of which can be utilised to synthesise the fuel or currency that is used by the body to perform work of various kinds. This currency takes the form of so-called energy-rich phosphate bonds ($\sim P$), notably those attached to the molecule of ATP (Adenosine Triphosphate).

So far our discussion has been in terms of the liberation of small packets of energy from the complex molecules but a more functional way to think of it is in terms of the creation of body energy (as $\sim P$) which can be used for a variety of purposes. The formation of each gram molecule of ATP from inorganic phosphate and ADP involves the capture of 10,000 calories of energy.

During aerobic respiration the total output of ATP from the degradation of a single molecule of glucose amounts to 38 molecules. These molecules of ATP incorporate in their energy-rich phosphate bonds 380,000 of the 690,000 calories contained in the original gram molecule of glucose. Consequently, the energy-capture efficiency of the whole process of cellular respiration is at least 50%. This is a good performance when it is remembered that engineers are reasonably satisfied when they are able to convert one-third of the heat of combustion of a fuel into mechanical work. In this comparison we have, of course, not considered the change from the ATP to the performance of mechanical work but apparently this is a very efficient process.

Thus far, then, we have seen that the cytochrome system is the vital link between the metabolic pathways of the body involving the degradation of large molecules and that the stepwise nature

of this degradation is designed to facilitate the synthesis of ATP molecules which can subsequently be used for the performance of mechanical work, biosynthesis, active transport, light production, etc.

(c) THE SUPPLY OF ATP

The different stages in the degradation of a glucose molecule are not all of equal value in the production of ATP molecules. The early parts of this process are usually termed *Glycolysis* and may take place in the complete absence of oxygen, ending in the production of two molecules of pyruvic acid from a single molecule of glucose. At this stage of the breakdown, only two molecules of ATP have been synthesised and therefore a mere 20,000 calories of the total 690,000 found in the glucose have been captured in a form which the body can use (i.e. only 3%). Under anaerobic conditions the pyruvic acid is converted into lactic acid which accumulates in the muscles or circulates round the body. Under aerobic conditions, however, pyruvic acid enters the so-called *tri-carboxylic acid cycle*. Furthermore, one of the hydrogen acceptors (DPN) involved in glycolysis is reduced, and under aerobic conditions can be oxidised via the flavoprotein-cytochrome system. Glycolysis of each molecule of glucose produces two molecules of this reduced nucleotide which when oxidised results in the production of six ATP molecules. Under aerobic conditions therefore the glycolytic cycle may be summarised as follows:

The remainder of the degradation of the glucose molecule takes place according to the process described as the tri-carboxylic acid cycle which involves *oxidative phosphorylation*. This process may be summarised as follows:

During this part of the cycle there are no less than 30 molecules of ATP synthesised. It is apparent, therefore, that the complete oxidation of a single molecule of glucose leads to the production

Fig. 38.

Diagram to show the main features of the breakdown of foodstuffs (based upon glucose) during aerobic respiration.

The reactions where CO_2 is liberated are indicated. Reactions in which substrates act as hydrogen donors to the cytochrome system are also shown. These are the places where molecular oxygen is utilised and energy captured in the form of energy-rich phosphate ($\sim P$) as ATP

of 38 molecules of ATP whereas anaerobic glycolysis produces only 2 molecules. These considerations emphasise the very great importance of the tri-carboxylic acid cycle together with the flavoprotein-cytochrome system. Both of these systems are now known to reside in the mitochondria of cells, but within these structures they are spatially separate. The cytochrome system is found on the surface of the membranes of the mitochondrion whereas the tri-carboxylic acid cycle enzymes are located in the matrix or soluble portion of the inner contents. The glycolytic enzymes are generally distributed throughout the cytoplasm.

(d) LACTIC ACID AND EXERCISE

From this very brief summary of the basic mechanisms concerned in the oxidation of glucose we can see that the production of lactic acid is a very inefficient process for producing bond-energy. Nevertheless, it has the advantage that it can take place under conditions when oxygen is in short supply or completely absent. At rest the body contains sources of readily available energy in the form of ATP and another phosphate-containing compound—*phosphagen*—which in vertebrates is creatine phosphate (CP). This compound is able to transfer its energy-rich phosphate bond to ADP and so produce a molecule of ATP. These reserves are, however, soon depleted during rapid exercise (ATP within 0.5 seconds, CP in about 5 seconds) and glycolysis makes a significant difference even although it is only capable of synthesising two molecules of ATP. Most of the extra energy required during exercise lasting between 10 seconds and 2 minutes is derived from anaerobic glycolysis. When the animal has finished the bout of exercise, the further oxidation of lactic acid via the tri-carboxylic acid cycle and cytochrome system may take place with the production of further molecules of ATP. Some of this ATP may be used to replenish the store of ATP and CP, and some for the performance of the chemical work of biosynthesis, a portion (5/6ths) of the lactic acid being converted back to glucose or glycogen in the liver. In other organisms, including some fish, there is no attempt to pay off the debt

incurred during the anaerobic stages and the lactic acid is excreted. This is true of fish such as carp. By contrast a trout pays off its oxygen debt when returned to normal environmental O_2 tensions.

During exercise the amount of lactic acid formed in man may be quite considerable. For example, 4 grams can be produced in a second, so that 40 grams will be accumulated by a sprinter at full speed over 100 yards. Such an athlete can tolerate the accumulation of about 127 grams of lactic acid in the body, whereas an average healthy man would have to stop when only half this amount had accumulated in his muscles. A sensation of strain or fatigue is closely related to the blood lactic acid concentration, and lactic acid can be looked upon as a 'fatigue toxin' in many instances. For each 6 to 7 grams of lactic acid, one litre of oxygen is required for the resynthesis of glycogen or glucose. Athletes can use between 4 and 5 litres of oxygen per minute. Long-distance runners inspiring $3\frac{1}{2}$ litres of O_2 per minute incur no debt at all, and they are apparently in a steady-state condition which can be maintained for $2\frac{1}{2}$ hours or more. Their ability to incur a debt of 16 litres of O_2 is extremely good and 19 litres is probably an absolute limit found in only very few athletes. From figures of this sort and a knowledge of the amount of O_2 required at different speeds, it is possible to calculate the distances which can be run at certain speeds and consequently the maximum speed expected on such a physiological basis over given distances in track performance.

The graph showing the decrease in speed attained over different distances (fig. 39) has a break at about 200 metres. Up to this distance the main factor limiting speed is the maximal contractile activity of the muscle. Oxygen uptake is unimportant because there is insufficient time for it to be transported from the lungs to the muscles. Nor over these short distances is the accumulation of lactic acid sufficient to limit performance. In middle-distance running the supply of energy is partly aerobic and partly anaerobic, the accumulation of lactic acid playing an important part in limiting performance. The aerobic and anaerobic mechanisms may well be independent of one another

so that steady running is not necessarily the best over these distances. Most of the better times over 440 yards have been done by running the first part much faster than the second. Payment of the 'oxygen debt' may not be wholly concerned with oxidising lactic acid, for this decreases slowly relative to the fall in the extra O_2 consumption. The extra O_2 may be used to re-synthesise energy-rich phosphate bonds from sources other than the oxidation of lactic acid.

Fig. 39.

Decline in speed with increase in distance run, plotted on the basis of world records in 1955 (after Bannister, 1960).

As we have indicated, long-distance running reaches a 'steady-state' with respect to aerobic respiration because the anaerobic processes contribute less and less to the total energy required as the distance increases. Anaerobic mechanisms probably contribute nearly a half of the total energy during a mile race, but less than a quarter for 3 miles. During such races the muscles may increase their O_2 consumption 50 times and this entails important modifications of the respiratory and circulatory systems. These result in increases of O_2 intake at the lungs, cardiac output (from 4–5 to 30–40 litres/min), and muscle blood flow.

The modifications during exercise of other vertebrates have not been studied in such detail. The speed of fish swimming is most rapid for short distances and they are well able to set up O_2 debts. Over longer distances respiratory and cardiac factors are more limiting. Lactic acid accumulation persists for a very long time (12 hours) after a period of rapid swimming and the increased O_2 consumption lasts for much shorter times. In animal studies it is difficult to be sure how 'hard the fish is trying' and in man there is no doubt that behavioural factors play an important part. As the first person to run a mile in under four minutes has written: 'Though physiology may indicate respiratory and circulatory limits to muscular exercise, psychological and other factors beyond the ken of physiology set the razor's edge of defeat or victory and determine how closely an athlete approaches the absolute limits of performance.' (R. G. Bannister, Chapter IX, *The Structure and Function of Muscle*, Vol. II. Academic Press, 1960.)

Conclusions

From this survey of the respiration of vertebrates several general conclusions can be drawn.

1. We cannot help but be impressed by the variety of mechanisms that are used to maintain the supply of oxygen to the tissues of vertebrates. They possess many adaptations which enable the physiological requirements of individual species to be met under very different conditions. These adaptations extend from gross differences in the basic structure of a gill and a lung to finer modifications of these organs to various ecological requirements.

2. The mechanism for the renewal of the medium at the respiratory surface is another feature which has been modified a great deal (Table 12). Throughout the vertebrates the respiratory current is maintained by two basic types of pump—*suction pumps* which draw the medium into contact with the respiratory epithelium and *pressure pumps* which force it across or into contact with these surfaces. Both mechanisms have advantages and the most efficient ventilation is achieved by fishes and birds which combine both systems and so maintain an almost uninterrupted flow of the respiratory medium.

3. In spite of paying detailed attention to such mechanisms we have also become aware of the necessity to consider the physiology of other systems. For example, we have needed to discuss the structure and physiology of the heart and circulatory system, the mechanisms of nervous co-ordination, the importance of water conservation and ionic regulation at the thin respiratory surfaces, and also nutrition which provides the different respiratory substrates and helps to maintain constant body conditions. The impossibility of considering one organ system in complete isolation is generally accepted in physiology, and for a comparative physiologist the principle is constantly before him

because he is aware of the correlation between changes in the function of these systems in different species.

TABLE 12
Vertebrate ventilation mechanisms

	<i>Pressure pump</i>	<i>Suction pump</i>	<i>Flow over respiratory organ</i>
Hagfish	Velum		Continuous
Lamprey		Branchial	Tidal
Selachian	Oro-branchial	Parabranchial	Continuous
Teleost	Buccal	Opercular	Continuous
Frogs	Buccal		Tidal
Reptile	Buccal?	Costal	Tidal
Bird	Costal (expiration)	Costal (air sacs)	Continuous
Mammal		Costal and diaphragm	Tidal

4. When comparing the structure and physiology of animals, a zoologist should consider the evolution of the systems under consideration. Functional continuity is just as characteristic of evolutionary processes as a sequence of structural modifications. In this instance a clear evolutionary change in the respiratory organs and circulatory systems has been established, and what is known of their physiology assists in the interpretation of these changes.

In order to summarise the main modifications that have been mentioned, the phylogenetic tree given on pp. 138–139 has been constructed. Some of the major changes in the evolution of vertebrates are indicated and it also serves to show the relationships of the different groups that have been mentioned in this book. Although there are many dangers involved in deducing relationships from the study of comparative physiology and morphology, a constant reference to the palaeontological record enables some of the major pitfalls to be avoided. It is from this point of view that a study of the functional morphology of vertebrates has considerable advantages over that of any other group.

Phylogenetic tree showing the major respiratory and the relationships of the groups that

changes during the evolution of the vertebrates
have been mentioned in this book.

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