THE CORRELATION OF STRUCTURE AND FUNCTION IN THE DEVELOPMENT OF THE NERVOUS SYSTEM.

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Catch phrases sometimes creep into scientific literature where their presence may be as insidiously suggestive of the possession of imaginary stores of knowledge as they are when employed in the description of current events. We have for example become so accustomed to affirming the history of the individual reproduces in miniature the history of the race that we are often in danger of assuming a greater degree of familiarity with the details of ontogenesis than is warranted by a careful survey of the facts. Our knowledge of the primitive reactions of the higher organisms in relation to synchronous structural conditions is still so meagre that it has scarcely risen above the stage of conjecture and cannot be presented in the form of organized experience. Although it is not necessary to actually question the validity of a very useful hypothesis, based upon the similarity of the more striking features in ontogeny that are paralleled by the chief events of phylogenetic development, there is nevertheless adequate reason for emphasizing the necessity not only for more careful study of the correlation of events in the structural and functional growth of the higher organisms, as fundamental to a more comprehensive understanding of the nature of nervous reactions, but also as a method of determining the factors of individual behavior.

Efforts have already been made by a few investigators to try and study the relationships existing between the structural conditions existing at certain epochs, and the character of the synchronous responses of the embryo. The observations of Wintrebert, probably among the first to be recorded in the discussion of these special problems, were not by any means as extensive or as carefully planned

as the work carried on by Coghill, which will unquestionably form a basis for future studies of importance.[1] Some of the results of my own observations along these lines have been referred to in three papers.[2]

Before attempting to continue the description of the details of my own investigations I wish to call attention to the variety as well as importance of the problems awaiting solution in this special field of enquiry. Many problems of phylogeny naturally suggest the consideration of questions relating to the correlation of structure and function. We find a parallel for the succession of events in racial development in the ontogenetic sequence or the life-history of the individual, in which are revealed a chain of phenomena much better adapted for detailed study than those occurring in the former and, what is of still greater importance, is that the latter are to a certain extent under the control of the investigator. The comparative rapidity with which individuals pass through the various stages in development is also a factor facilitating enquiry.

What is particularly needed at present is a careful systematic study of the initial responses in the lives of embryos, representing several different species of animals, and a record of these phenomena which is sufficiently detailed to indicate the relationship existing between the physiological events and the changes taking place within the nervous system. Unfortunately investigators have long been hampered by the compelling desire to attempt to solve the problems relating to the complex nervous system of the adult before considering the simpler correlations possible in the early life of the embryo.

Among the primitive adjustments of all organisms those for temperature variations naturally play a very important rôle, and this is only what might be inferred when we reflect upon the fact that the responses of living beings to heat and cold are fundamental properties of all living matter. The reactions recurring in response to thermic stimuli, before the development of the nervous system, present some interesting features. It has long been known that

[1] *J. Comp. Neurol.*, Vol. 19, 1909.

[2] *Mittheil. a. d. Zoolog. Station*, 2, Neapel, 18 Bd., 2–3 Hft., 1907; *J. Comp. Neurol.*, Vol. 21, No. 4, August, 1911; *J. Experiment. Zool.*, Vol. 11, No. 4, Nov., 1911.

living embryos when placed in various solutions respond with great rapidity to even relatively slight temperature changes occurring in the surrounding media. In the case of the pulsation of the heart many investigators, among whom are Snyder, Carlson, v. Tschermak, and others, determined the temperature coefficient in connection with the activity of this organ. As far as I have been able to determine the extreme sensitiveness of the heart as regards rises in temperature seems to be somewhat greater, or at least the responses are quicker, at a period when the development of the nervous system is well advanced than at earlier stages in the life of the embryo; and I believe the same law holds true with regard to other reactions of the organism. These facts afford an interesting confirmation of the results of observations made by A. G. Mayer with a view to determining the relative importance of the nervous system in the medusa. Mayer has shown that there is greater sensitivity for heat when the muscles remain in contact with the sense-organs than when the connections are severed. The general character of the responses of the embryo in regard to heat, prior to or subsequent to the development of the nervous system, are in a measure comparable to the variations of adjustment of jellyfish for similar stimuli when muscles are either deprived of connection with or allowed to remain in contact with sense organs. In the vertebrate embryo as well as in the medusa the extreme delicacy of response is dependent upon the presence of nerve-elements, and when these have not developed or have been eliminated by experiment the capacity of adaptation of the organism is correspondingly lowered.

The technique used in the experiments is the same in all cases. The chief precaution necessary is to avoid as far as possible subjecting the embryos to changes in temperature and all rough handling; so that the results may not be complicated by the introduction of too many different stimuli.

When the eggs are taken out of the incubator they are opened as quickly as possible, just inside the door of the warm box which covers the microscope, and the embryos are detached from the egg and lifted by means of a horn spoon into the dish containing the solution ($NaCl$ 0.9 — $CaCl_2$ 0.02 — KCl 0.02 — $NaHCo_3$ 0.02 —

glucose 1 per cent., bouillon 10 per cent.). After a little practice the operation of removing the embryo from the egg and placing it in the dish, without either delay or unnecessary shock, may be easily performed. It is obvious that stimuli of a purely mechanical nature up to a certain degree of intensity seem to be less injurious than those caused by variations in temperature.

The effect of rapid changes in position upon the action of the heart during the period represented by embryos of from 12–16 somites is almost a negligible quantity. Embryos that were whisked rapidly about in a dish by means of a camel's hair brush showed no disturbance of cardiac activity; provided of course that the temperature of the solution in which they were placed remained constant.

The primitive responses of these organisms show certain interesting features when elicited in response to various chemical substances used as irritants. In this connection the action of a number of different substances was observed, while that of two was studied in detail. The substances selected for more detailed investigation were strychnia sulphate, an important inorganic nerve stimulant, and thyroid extract, representing organic substances toxic for nervous tissues. After it became possible to eliminate the error attributable to such slight differences in temperature as are apt to occur during manipulation it was found that these two dissimilar substances were strikingly alike in their physiological action upon the heart, if used at a time prior to the development of the nervous system. Even when employed in minute quantities the characteristic accelerating action upon the heart was not observed. As will be noticed in studying the records in the case in which the smallest doses were administered the rate of the cardiac pulsations was not disturbed for some time and only after the elapse of from one to two hours did the action of the heart begin to show symptoms of sagging. In all cases an accelerating action seemed to be entirely absent.

Probably the most intimate correlation which we have yet been able to establish is in connection with the development of the peripheral nervous system. In the case of such substances as cocaine and eucaine we have already shown (*op. cit.*) that there is no inhibitory and reversible action in selachian embryos following ordinary

doses of these drugs until the peripheral nervous system is developed. We find the action of thyroid extract as well as strychnine is modified to some extent by the development of the sympathetic nervous system; an occurrence taking place about the fourth day. We are not yet prepared to state exactly what the character of this mechanism is, although for the present we may consider it highly probable that the increased activity of the heart brought about by moderate doses of the two substances mentioned is the result of the functional activity of the sympathetic system. The symptoms of irregularity in the heart's activities which develop after a certain period deserve consideration and show a remarkable degree of similarity for both strychnia, thyroid extract and magnesium chloride. As will be noticed in chick no. 3 the rapidity of the heart decreased after the embryo was placed in a solution containing thyroid extract. Suddenly, and this seemed to be the characteristic effect of all the substances used—the organ stops pulsating, remaining motionless for a period varying, as a rule, from ten to thirty seconds, or even two minutes. Then it suddenly begins to pulsate again, the rhythm gradually increasing in strength and rapidity until a point of maximum intensity is reached and then after one-half or one minute the cycle ends again. The abrupt manner in which the pulsations cease and the subsequent incidence of the beats, often after prolonged intervals of rest, are strikingly similar to the phenomena taking place when an embryo has been poisoned by an excess of magnesium chloride. In these early stages of development it is extremely interesting to compare the action upon the heart of three substances, possessing chemical qualities as different as thyroid extract, magnesium chloride and strychnine sulphate. The characteristic primary toxic effects as shown in the adult by the rapid rhythm of the heart do not appear until the period when the nervous system has attained a relatively high degree of differentiation.

In addition to the substances already mentioned, solutions of NaOH (1:500) and CH_3OOH (1:500–1:1,000) were employed. No positive results, except a gradual slowing of the heart, were noted in connection with the former, but the latter seemed to exert a marked inhibitory action upon the heart; the stronger solutions

rapidly, and the weaker ones slowly but surely blocking the rhythm. Solutions of adrenaline (1 : 4,000) and epinine (1 : 2,000) produced symptoms similar to those following the use of thyroid (1 : 10,000).

Some of the details of the experiment are given in the following records:

Chick No.	Somites.	Time.	Heart-beats.	Solution.	Results.
1	13	10.7 A.M.	54	Ringer and (1:500)CH_3OOH	
		.11	66		
		.25	—	——	No heart beats.
2	15	12.26 P.M.	96	Ringer and (1:1000)CH_3OOH	Temperature of fluid above normal.
		.28	69		
		.31	78		
		.33	66		
		.40	78		Rises and falls in heart rate due to temperature changes.
		.45	66		
		.47	75		
		.50	70		Contraction of heart was shallow and snappy.
3	13	10.17 A.M.	52	Ringer and Thyroid (1:10,000) at 10.22	
		.23	48		
		.30	48		
		.45	48		
		11.06	51		
		.16	48		
		.57	51		
		12.31 P.M.	54		
		1.00	44		
		.35	36		
		2.11	33		Pulsations very weak but regular.
4	13	3.50 P.M.		Ringer's solution alone	
		.54	26		
		4.00	42		
		4.20	42		
		.57	42		
		5.35	42		
		.47	42		Heart beating very feebly.
		9.30	60		
5	14	4.35		Ringer and Thyroid (1:15,000)	
		.37	72		
		5.00	72		
		.44	60		
		.53	60		
		10.00	48		Individual pulsations strong, but broken by periods of complete rest.

The special instances which we have cited are a few taken from a long list of experiments and the results as given may be considered to be characteristic of all the cases observed. It is quite unnecessary to repeat in detail the experiments in which strychnia sulphate was used as the results for solutions varying in strength from 1 : 5,000 to 1 : 10,000 practically corresponded with the records for thyroid extract.

An extremely interesting field of work lies in the direction of determining with more exactitude than has yet been done the varying degrees of responsiveness of the organism to these toxic agents at different periods in the early development of the embryo. An exceedingly complicated problem but one of great importance would be the determination, if possible, of the change in the symptoms as the embryo develops and the probable progressive increase in the permeability of the cells for the different solutions. This question must be solved before we can appreciate the character of the changes in the reactions taking place within the organism when the control of functions is taken over by the nervous system.

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