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Estudios sobre la dinámica de la morfogénesis y herencia en la
reproducción experimental.

XI. Factores fisiológicos en el desarrollo de la cabeza de la planaria.

Las diferentes formas de cabeza observadas hasta el presente en la reconstrucción de trozos de *Planaria dorotocephala* pueden distribuirse en dos grupos principales. Esta serie, que comprende diversas condiciones desde la normal hasta la acéfala, representa una serie de inhibiciones diferenciales del desarrollo, siendo la inhibición mayor en la región media, decreciendo lateralmente. Bajo ciertas condiciones pueden tener lugar cambios secundarios en la forma de la cabeza, en dirección opuesta a las inhibiciones diferenciales. Estos cambios son el resultado de la aclimatación diferencial a la acción del factor inhibidor o de la regeneración diferencial después de su acción. El desarrollo de todos los términos de esta serie puede influirse experimentalmente mediante la acción de factores externos físicos y químicos y de factores fisiológicos internos. Las diferentes formas de cabeza están determinadas no por la acción específica de los agentes particulares o las condiciones del protoplasma, sino por el cambio de la condición fisiológica del protoplasma, la cual es fundamentalmente cuantitativa. La acción regional diferencial de los agentes físicos y químicos es el resultado de la presencia de gradientes fisiológicos en el protoplasma. Faltando dichos gradientes, una serie gradual de formas de cabeza diferencialmente inhibidas, desde la forma normal hasta la acéfala, sería imposible. La presencia o ausencia de órganos particulares en estas cabezas, como por ejemplo, los ojos, no supone la presencia o ausencia de los factores hereditarios o de las potencialidades correspondientes, sino simplemente la existencia de diferencias, primordialmente cuantitativas, en las condiciones necesarias para la realización de las potencialidades hereditarias.

STUDIES ON THE DYNAMICS OF MORPHOGENESIS AND INHERITANCE IN EXPERIMENTAL REPRODUCTION

XI. PHYSIOLOGICAL FACTORS IN THE DEVELOPMENT OF THE PLANARIAN HEAD

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THIRTY-THREE FIGURES

Earlier papers of this series and several other papers have dealt with various aspects of the reconstitucional development of *Planaria dorotocephala* in relation to experimental and physiological conditions. It has been shown that development may be altered and controlled within very wide limits (Child, '09, '10 a, b, '11 a, b, c, '14 b, '16 a, '20 a) and that widely different developmental results, ranging from normal development to complete absence of certain organs or organ complexes and including different localizations and proportions of parts and organs, may be determined and controlled by physiological changes determined in a quantitative, rather than a specific way (Behre, '18, Child, '11 a, '14 b, '16, '20 a). The head has proved be of particular interest in these experiments, because of the possibility of experimental control and modification of the development of this most highly specialized region of the body with the production of a graded series of head-forms ranging from the normal to complete absence.

Experiments of various investigators have shown that very small pieces of the planarian body may give rise to heads alone. These facts demonstrate that the head is able to develop in the complete absence of other parts. This is true not only for *Planaria*, but for other relatively simple organisms in which re-

constitutional development of a head or apical end occurs (Child, '15 b, chap. IX). Moreover, the head is the chief organ of physiological dominance or control, in short of physiological integration (Child, '10 b, '11 c, d, 12, '15 b, chap. IX), it represents the high end of the chief physiological gradient in the body (Child, '13 b) and finally the graded series of head-forms, ranging from normal to complete absence, may be determined and controlled by many different agents and conditions, both external and physiological. The present paper is primarily concerned with the problem of head-development in its relations, on the one hand, to these experimental and physiological conditions and, on the other, to the hereditary constitution of the protoplasm.

HEAD-FORM AND HEAD-FREQUENCY IN RELATION TO EXTERNAL AND INTERNAL CONDITIONS

It has been pointed out in various papers (Child, '11 a, b, '15 b, pp. 105—108) that a series of head-forms exists in the reconstitution of pieces of *Planaria dorotocephala*. The terms of this series have been separated for convenience into the groups: normal, teratophthalmic, teratomorphic, anophthalmic, and acephalic. These different forms of head, briefly described in earlier papers and considered more fully below, evidently represent various degrees of inhibition of head-development, ranging from the very slight degree of inhibition in the teratophthalmic to the complete inhibition of the acephalic form. It has also been shown that in material which is physiologically standardized as far as possible as regards physiological age or size and nutritive condition, pieces with anterior ends at a given level of the body show a decrease in head-frequency with decrease in length of the piece (Child, '11 a, b, d). Second, comparing pieces of the same length from different levels of the body, we find that head-frequency is highest at levels nearest the original head and decreases as the level of the cut surface becomes more and more posterior, back to the level of fission, where the head-frequency suddenly increases again (Child, '11 b, d). Posterior to the usual level of fission the different zooids are physiologically

more or less clearly indicated by the differences in head-frequency at different levels (Child, '11 d). In pieces representing the same fraction of body-length the head-frequency is lower in smaller, physiologically younger animals than in larger, older animals and lower in starved than in well-fed animals (Child, '11a, '20 a). In pieces of like size from animals of the same size and in the same physiological condition, the head-frequency is higher in pieces excited to active locomotion during the early stages of reconstitution than in pieces remaining undisturbed (Child, '11a, '20 a).

On the other hand, it has been possible to control and alter head-frequency by means of various external physicochemical factors. KNC, for example, decreases head-frequency at levels near the head and, except in relatively high concentrations, increases it at levels near the posterior end of the first zooid and produces little change at intermediate levels (Child, '16 a). Extensive work by Mr. J.W. Buchanan, which is not yet published, shows that various anesthetics act in essentially the same way as cyanides on head-frequency. Some work not yet completed, with agents which act chiefly as accelerants rather than inhibitors indicates that such agents alter head-frequency in the opposite direction from the inhibiting agents. And finally, experiments with different temperatures have shown that both high and low temperature are very effective in altering head-frequency (Behre, '18). Most of these experiments have been used in laboratory class work and have therefore been repeated by many different persons, with essentially identical results. In general the inhibiting agents decrease head-frequency in pieces from regions near the head, where it is normally highest, and increase it in pieces near the posterior end of the first zooid, where it is normally lowest. It has been shown by increase in susceptibility and in CO_2 production that the pieces are temporarily stimulated by the act of section (Child, '14 a, Robbins and Child, '20), and data on oxygen consumption obtained by Doctor Hyman and soon to be published also demonstrate this stimulation. The data on stimulation show that in pieces of given length, the stimulation is least at levels nearest the

head and greatest at levels nearest the posterior end of the first zooid, pieces from intermediate levels showing intermediate degrees of stimulation (Child, '14 b) and that in pieces of different length with anterior ends at the same level, the shorter pieces are more stimulated than the longer. And finally, it has been shown that it is determined during this period of stimulation following section whether or not a piece shall give rise to a head (Child, '14 b), and that the greater the degree of stimulation, the lower the head-frequency (Child, '14 a, b). According to the experimental data, then, this stimulation of the pieces following section inhibits rather than favors head-development. As pointed out elsewhere, this relation between head-frequency and stimulation of piece enables us to understand how the same concentration of an inhibiting agent such as KNC may alter head-frequency in two opposite directions. First, it may inhibit to a greater or less extent the activity of the cells directly concerned in head-development and so decrease head-frequency. Second, it may inhibit or decrease the stimulation following section, i.e., it may inhibit the physiological factor which inhibits head-formation and so may actually increase head-frequency under certain conditions (Child, '16 a). In the same paper it was shown that relatively short exposures to the agent, which merely prevent the temporary stimulation and permit recovery of the head-forming cells are more effective in increasing head-frequency, while exposures continuing through a considerable part of the head-development are more effective in decreasing head-frequency. This is of course to be expected from the facts.

The data of experiment in general force us to the conclusion that head-development is not determined by other regions of the piece, though it may be inhibited by them. Head-development is a self-differentiation which occurs if the cells near the cut surface undergo a sufficient degree of dedifferentiation and attain a sufficiently high rate of metabolism. In pieces undergoing reconstitution, whatever the level of the pieces the head arises directly from the cut surface, and it is evident that in all cases except at levels directly behind the original head, the

new head is out of place and develops at the expense of whatever regions of the body adjoin the cut surface. In fact, it may be said to develop in spite of other parts of the piece, and the more intense the stimulation of these parts, the less rapid and complete is the dedifferentiation of the cells at the cut surface and therefore the greater the degree of inhibition of head-development.

Under all conditions thus far analyzed, whether these are internal, such as region of body, degree of stimulation, nutritive condition, and physiological age, or external physicochemical conditions, the series of head-forms from normal to acephalic is essentially the same. In other words, there is no evidence to indicate any specific relation between particular head-forms and particular conditions or agents. Slight minor differences with different agents may indicate specificities, but it is perfectly evident that the series of head-forms in general represents quantitative gradations rather than specific differences in developmental factors.

DIFFERENTIAL SUSCEPTIBILITY

It has been demonstrated for several hundred species of organisms, including the chief animal groups as well as many plants, that from the earliest embryonic stages on, definite and characteristic differences in susceptibility are related in a definite way to the physiological axes (Child, '20 b, pp. 154-162, and references there given). Moreover, it has been found that in general among the simpler organisms and in the earlier stages of development susceptibility to a certain range of relatively high concentrations or intensities of at least many external agents varies directly, though not necessarily proportionally, with the rate of certain fundamental physiological activities and that the ability to become acclimated to certain lower ranges of concentration and to recover from temporary exposure varies in the same way. This relation between susceptibility and physiological condition is fundamentally quantitative in character. In the more highly differentiated stages and organisms this simple relation is altered and complicated by various, ap-

parently specific relations between particular organs or tissues and particular agents. Many different lines of evidence indicate that the physiological axes are primarily quantitative gradients in physiological condition and metabolic rate and that the differential susceptibility at different levels of an axis results from this difference (Child, '20 b). The region from which the head, or apical end develops, being primarily the most active region, is most susceptible to higher and most capable of acclimation to lower concentrations and intensities of external agents. It has been demonstrated in various ways that this relation holds good for the head of *Planaria* (Child, '11 c, '12, '13 a, b, '16 a).

It has also been shown that differential susceptibility, besides determining different survival times of different regions, determines developmental modifications in two opposite directions, differential inhibition on the one hand and differential acclimation or recovery and in some cases differential acceleration on the other (Child, '16 b, '17; Bellamy, '19). The graded series of head-forms in *Planaria* is evidently the result of a non-specific action, since all terms of the series are produced by many different external and internal conditions. Moreover, since different regions of the head are affected in different degree in the different forms, a differential action of the determining factor or factors is evidently concerned. It remains, then, to be determined whether, or to what extent, the series of head-forms can be interpreted in terms of differential susceptibility.

DIFFERENTIAL INHIBITION IN HEAD-DEVELOPMENT

The normal head. The normal head of *Planaria dorotocephala* (fig. 1) possesses certain rather definite characteristics as regards external form localization of sense organs and position, form and structure of the cephalic ganglia. The ganglionic mass, unquestionably the primary organ of the head, is in the normal head, distinctly double, consisting of right and left halves, connected by a commissure. The same bilaterality is also evident in the localization and innervation of the sense organs

Figures 1 to 4

and in the form of the head. Obviously, the normal head represents a certain proportionality of parts which in some way is determined as the usual result of development.

The teratophthalmic head. The shape of the head is normal, but the eyes show more or less approximation to the median line, and section shows that the ganglia are also more or less approximated with reduction or complete absence of the commissure between them (fig. 2; also Child and McKie, '11). Figure 3 shows some of the eye-forms characteristic of the teratophthalmic head, the first five horizontal rows of the figure representing bilaterally symmetrical, the last two rows asymmetrical forms. The first four rows show forms in which more or less continuity of pigment appears, even when the eyes are a considerable distance apart. In the fifth row are shown cases in which the pigment cups remain distinct until the eyes are rather closely approximated. The order in each series follows in general the degree of departure from the normal eye-form. The asymmetry of the series in the last two rows of figure 3 is the result of purely incidental factors which determine a difference in rate of development on the two sides of the median line. For example, obliquity of cut surface may determine temporary asymmetry, the more posterior levels developing more slowly because they represent lower levels of the longitudinal gradient. Again, if the amount of entodermal tissue exposed at the cut surface is much greater on one side than on the other, the exposure of parenchyma is less and the rate of head-development is slower on the side with the greater entodermal exposure. The asymmetries of the eyes in this series are merely indications of the ganglionic asymmetries. In many cases both disappear in later development.

It is evident that the teratophthalmic head differs from the normal in the reduction or complete inhibition of the median region of the head, at least at the level of the ganglia. The degree of inhibition may range from the just appreciable approximation of eyes and ganglia to the complete inhibition of development of the region lying between the dotted lines in figure 4. Whether the inhibition of the median region extends to the tip of the head

cannot be determined with certainty because of the absence of well-defined landmarks in this region, but the conditions found in the teratomorphic heads make it probable that at least in the more extreme teratophthalmic forms the median region is more or less inhibited throughout the whole length of the head.

The series of dotted lines in figure 4 are intended to represent in a diagrammatic way approximately the regions inhibited in various degrees of teratophthalmia. At the level of the ganglia the degree of median inhibition can of course be determined with relative exactness by the degree of approximation of the eyes and in section of the ganglia. As regards the preganglionic region, however, the lines in figure 4 are merely suggestive.

Since the teratophthalmic head-form is determined by external and physiological conditions which retard or inhibit head-development to a greater or less degree, it is obviously a result of differential inhibition, the median region of the head being more susceptible and therefore more inhibited than the lateral regions.

The teratomorphic head. This is merely a more extreme degree of differential inhibition. This head-form usually shows a single median eye (figs. 5 to 8) and a ganglionic mass retaining only slight traces of the double structure of the normal ganglion (Child and McKie, '11). Here the differential inhibition evidently includes the median head region all the way to the tip, for this region is more or less completely absent, and therefore the cephalic lobes, lateral in normal heads, appear farther anteriorly and more or less approximated to the median line, until in the more extreme forms a single median cephalic lobe with double (fig. 7) or even single unpigmented sensory area at its base figure 8, develops. In these cases the whole triangular region of the head between the cephalic lobes has failed to develop. Figure 9 indicates diagrammatically the regions chiefly inhibited in the various degrees of teratomorphic development.

There is some overlapping as regards the eyes between teratophthalmic and teratomorphic forms. Occasionally in heads distinctly teratomorphic as regards other features, more or less distinctly double, instead of single eyes appear, and heads which

Figures 5 to 14

are normal as regards position of cephalic lobes and preganglionic development show only a single eye.

The anophthalmic head. This represents a still more extreme stage of differential inhibition, the eyes and usually the cephalic lobes being absent and the ganglionic mass remaining rudimentary. Externally the anophthalmic head usually remains without distinguishable organs of special sense (figs. 10, 11), though sometimes a partially double or wholly single cephalic lobe appears at the tip (figs. 12, 13). Except in some cases of very slight development of new tissue, behavior of anophthalmic animals differs distinctly from that of acephalic forms, being more like that of forms with more highly developed heads, and section shows at least a rudimentary ganglion. As indicated in figure 14, the anophthalmic head represents almost complete inhibition of head development.

The acephalic form. Here development of a head is completely inhibited, the cut surface contracts, the wound is merely filled in with cells, and healing occurs without outgrowth (figs. 15, 16). Even here, however, differences in the contraction of cut surface and amount of new tissue appear in different headless pieces, as figures 15 and 16 indicate. Such differences are of course dependent on the degree or completeness of inhibition of outgrowth.

This series of head-forms from normal to acephalic evidently represents different degrees of differential inhibition. The differential between median and lateral is clearly marked, the median region being most susceptible and so most inhibited and susceptibility decreasing laterally. The longitudinal differential also appears to some extent, the ganglionic region being the most susceptible region, but the difference between it and the preganglionic region is slight. In consequence of these susceptibility differentials, inhibition of head-development involves first the median ganglionic region and then progressively the anterior and lateral regions, until head-development is completely inhibited. It must be remembered that the differential susceptibility determining the different head-forms is that of the earlier stages of head-development, and that the susceptibility relations during

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Figures 15 to 21

stages are not wholly identical with those of the fully developed head with its specialized sense organs. The facts indicate that the ganglionic region is primarily the region of highest susceptibility in the whole head and that the preganglionic region arises as a secondary gradient in the opposite direction from that of the rest of the body. Apparently similar conditions exist during development in at least many other animal groups, even the vertebrates, the most susceptible region during all except perhaps the earliest stage being not the extreme anterior tip of the head, but a somewhat posterior level. Such secondary gradients arise during the course of development and may even disappear later, but it is difficult to determine with certainty how far later changes in susceptibility to particular agents are due to quantitative differences in physiological condition and how far to specific relations. Only when it has been found that, as in earlier stages, the susceptibility relations are essentially the same for a given range of concentration or intensity of many different agents is it reasonably certain that the relations are primarily quantitative rather than specific.

DIFFERENTIAL ACCLIMATION AND RECOVERY IN HEAD DEVELOPMENT

Under conditions which permit acclimation or recovery to occur, we find indications of differential effect similar to those already observed in other forms (Child, '16 b, '17; Bellamy, '19); that is, the changes are in the opposite direction from those involved in differential inhibition. Some of these changes observed are briefly described.

Differential acclimation in normal heads. When intact animals with normal heads (fig. 17) are placed in low concentrations of various anesthetics, e.g., ethyl alcohol 1.25 to 1.5 per cent; ethyl ether 0.2 to 0.4 per cent, the solutions being renewed every two two days or oftener, the whole head decreases in size relatively to the body, but the preganglionic region undergoes more or less complete reduction, either by resorption or disintegration, until after sixteen to twenty days the head resembles figure 18. About this time, however, or soon after, new growth begins in the median

portion of the preganglionic region, in the same solution which brought about the earlier reduction of this region, and ten to fourteen days later, that is, a month after the animals were first placed in the solution, the heads range in form between figures 19 and 20. The whole head has undergone increase in size, but the median region has grown much more rapidly than any other part and has given rise to a disproportionately large preganglionic region. This region is functional and is bent and twisted about in locomotion: it very evidently represents merely an overdevelopment of the median preganglionic region with its sensory margins. Its development can mean nothing else than that the cells of the median region become, after a certain length of time in the solution, more capable of growth than those of the more lateral regions and that under these conditions the median region grows to larger than normal size because its ability to use nutritive material and to synthesize new protoplasm is relatively greater as compared with that of lateral regions, though actually of course less than in the normal animal. In other words, the alteration of size and proportion means an alteration in the metabolic relations of median and lateral regions in consequence of differences in their susceptibility and capacity for acclimation.

Animals with heads like figures 19 and 20, when removed from the anesthetic solution to water, show a gradual approach to the normal head-form. After two months in water some heads may be nearly normal, but the preganglionic region is usually still somewhat larger than normal. It is probable that completely normal proportions would be reached in time, but none of these experiments was continued longer than two months after return to water.

Differential acclimation in development of new heads. When pieces undergo reconstitution in alcohol (1.25 to 1.5 per cent) or ether (0.2 to 0.4 per cent) or in low concentrations of chloretone or of various other anesthetics, the development of the head is at first markedly inhibited. A very common form of head under such conditions is that shown in figure 22. Here the outgrowth of new tissue at the cut surface is largely inhibited, but rediffer-

entiation has occurred behind this surface and a single median eye has developed. If differentiation proceeded far enough, such a head would undoubtedly be teratomorphic. This form of head develops in a week or ten days, but after two weeks or more, even though kept in the anesthetic, further development usually occurs, resulting in a form with overdevelopment of the median region like figure 23, or sometimes in a head of normal or nearly normal form (fig. 24). Figure 23 shows the same type of head as figures 19 and 20. This head-form is, in fact, characteristic of conditions which inhibit head-development at first, but permit some degree of acclimation.

Figures 23 and 24 show another interesting feature. In the earlier stages these heads possess a single median eye, but when acclimation and further development take place, two more eyes appear in normal position, so that the head finally possesses three eyes. This must mean that in the earlier development the median head region is so far inhibited that conditions determining differentiation of eyes exist only at the median line. The region between the eyes of normal heads is completely inhibited. Later, when acclimation occurs, the median regions develop further and eyes and nerves develop in normal relations. The less inhibited and more completely acclimated heads approach normal form, except as regards the median eye (fig. 24), while less complete acclimation gives forms like figure 23. These latter, however, if returned to water, gradually approach normal proportions.

Secondary transformation of teratomorphic heads. The teratomorphic head apparently represents a rather unstable equilibrium, for its frequency is usually much lower than that of other head-forms, and heads which at first develop as teratomorphic not uncommonly undergo transformation after a week or two into teratophthalmic forms. This transformation may occur in water at room temperature, as well as in cases of acclimation to inhibiting external conditions. Figures 25 to 28 show heads which were originally teratomorphic heads resembling those of figures 5 and 6. The transformation involves changes in both the cephalic lobes and the eyes, besides the internal

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Figures 22 to 33

changes. The original cephalic lobes are resorbed or atrophy and new ones develop in normal position. In figure 25 the old disappearing lobes are indicated near the tip of the head. In the stage figured here the lobes as actual outgrowths have already disappeared, the two areas indicated in the figure representing the unpigmented sensory areas at the base of each lobe. The eye changes consist either in the development of two complete eyes in addition to the median eye (figs. 25, 26) or in various degrees of teratophthalmia (figs. 27, 28), and the median regions of the ganglia also develop more or less completely. Such transformation has been observed repeatedly in all its stages. It occurs chiefly in the less extreme teratomorphic types, such as figures 5 and 6, the more extreme types (figs. 7, 8) being in most cases permanent.

As pointed out above, the teratomorphic head results from inhibition of the median regions to a certain degree, and it is evident that the secondary transformation of such heads represents more or less complete acclimation to, or recovery from, the earlier differential inhibition; that is, the median regions at first inhibited, later undergo more or less complete development.

Secondary transformation of anophthalmic heads. Heads which develop at first as anophthalmic heads of ordinary form (figs 10, 11) very often show secondary elongation, particularly of the median region (figs. 29 to 31), and in some cases a median cephalic lobe develops at the tip (fig. 32) and occasionally after two or three weeks a single median eye (fig. 33); i.e., the anophthalmic may in some cases become secondarily a teratomorphic head. Here again it is evident that the secondary transformation results from growth and often hypertrophy of those head regions which were at first most inhibited.

Secondary transformation of acephalic forms. Such transformation is also of very frequent occurrence in acclimation to, or recovery from, inhibiting factors. Pieces which remain acephalic indefinitely under the inhibiting conditions may develop anophthalmic, or in some cases teratomorphic, and occasionally even teratophthalmic heads when acclimation or recovery occurs. Acclimation usually results in forms like

figures 29 to 33, while in recovery after removal of the inhibiting factor the more nearly normal head-forms may appear. In temperature experiments, for example, pieces which remain acephalic for several weeks at low temperature (3° to $5^{\circ}\text{C}.$) sometimes begin to develop anophthalmic or teratomorphic heads after this time, even when kept at the low temperature, but if removed to $20^{\circ}\text{C}.$ many develop teratophthalmic and some even normal heads.

DIFFERENTIAL SUSCEPTIBILITY IN DEVELOPMENT IN GENERAL

It will be noted that in the heads of *Planaria*, as well as in the development of the sea-urchin (Child '16 b), the polychete (Child, '17) and the frog (Bellamy, '19) departures from the normal occur under the experimental conditions employed in two opposite directions. In the differential inhibitions certain regions are affected to a greater degree than others, and the parts to which the regions most affected normally give rise are more or less reduced or completely absent. In the differential acclimations and recoveries the parts originally most inhibited develop more or less completely or may even show over-development. The most extreme types of differential acclimation (figs. 19, 20, 23) have thus far been observed only after the use of external agents which produce at first marked inhibition, but in which a considerable degree of acclimation occurs. The habit-forming inhibiting drugs, for example, so far as they have been used, are particularly favorable agents for the appearance of these secondary changes. In cyanide, on the other hand, in which acclimation is very slight and occurs very slowly, the more extreme acclimation forms have never been seen. All other head-forms except these extreme acclimation forms, not only the differential inhibition series normal to acephalic, but the less extreme acclimation forms, can be and have been determined by all of the external chemical and physical agents used in my experiments, as well as by the physiological conditions associated with differences in size of piece, region of body, nutrition, age, etc. These head-forms are, in short, the morphological effects of physiological

changes which are non-specific; that is, quantitative in character. The same is true of the differential inhibition and acclimation forms in sea-urchins and polychetes. Moreover, even in the vertebrates similar developmental modifications may be similarly produced. In the frog, for example, Bellamy has produced experimentally a series of differential modifications of development essentially similar to those in *Planaria* as regards axial relations. The differential inhibitions of head-development range from normal to almost acephalic, through a series of forms closely comparable to those in *Planaria* in that they all represent a greater degree of inhibition of median than of lateral regions. The differential acclimations and recoveries, on the other hand, represent changes in the opposite direction. Only some of the data on the earlier stages have as yet been published (Bellamy, '19). It is also evident that the cases of cyclopia experimentally produced by Stockard ('07, '09, '10, '11) in fishes are cases of differential inhibition similar to those in *Planaria* and other forms. In these cyclopias the median region of the head is more inhibited in early developmental stages than lateral regions. The intermediate forms between the complete cyclopias and the normal heads are closely comparable to the various degrees of differential inhibition in the planarian head. The occurrence of essentially similar developmental modifications in such widely different organisms and under so wide a range of experimental conditions indicates the existence in all these forms of certain non-specific or quantitative physiological factors concerned with the localization, growth, and differentiation of parts. These factors are, as so often pointed out, the physiological gradients. The median region of the head is, on the one hand, more inhibited than lateral regions and, on the other, acclimates or recovers more rapidly or more completely, because it represents the 'high' region of a physiological gradient; i.e., a region differing in its physiological state from other levels of the gradient in such manner that the rate of the fundamental metabolic reactions is higher in it than at other levels. Similar gradients of this sort may exist in protoplasms which are specifically very different, and their existence determines

the similarity of the differential modifications of development in different species and accounts for the fact that they represent a quantitative rather than a specific aspect of the action of physical and chemical agents upon protoplasms. In other words, these modifications result primarily from differences in rate, amount, intensity, or degree, etc., in protoplasm, rather than from differences in quality, but in so complex a physicochemical system as protoplasm qualitative differences are certainly frequently determined by quantitative changes. There can be no doubt, for example, that rate of fundamental metabolism in the cells which give rise to a new head in *Planaria* is one factor in determining whether or not eyes or cephalic lobes or even cephalic ganglia shall develop.

The significance of the physiological gradients has to do with these quantitative aspects of development. They represent merely quantitative physiological conditions in the protoplasm, which constitute factors in the realization of the hereditary potentialities of that particular protoplasm. The gradients create nothing; they do not determine the specific characteristics of particular organs; they merely determine whether a particular process of realization shall occur or where it shall be localized and how it shall proceed.

The fact that essentially the same developmental modifications may be produced by many different agents and conditions does not, of course, mean that all such agents and conditions act in exactly the same way upon protoplasm. It means merely that with certain ranges of intensity or concentration non-specific factors or quantitative factors in their action exist. It is these factors which constitute the basis of differential susceptibility. Undoubtedly different agents and conditions act in different ways upon the same protoplasm and the same agent or condition acts in different ways on different protoplasms, even upon different organs or tissues within the same individual. Notwithstanding these real or apparent specificities of relation between protoplasm and physicochemical agents, the non-specific aspects also exist, and in the simpler organisms and the earlier stages of development they play the larger part.

And finally, the fact must be emphasized that differential inhibitions, acclimations, and recoveries in development are dependent primarily upon the differences in susceptibility in the earlier developmental stages, rather than upon those observed in the fully developed animal. In *Planaria*, for example, as in other forms thus far examined, the data indicate very clearly that in the earlier stages of head-development the median region is more susceptible to higher and more able to acclimate to lower concentrations and intensities than lateral regions. In the fully developed normal head, however, the special sensory regions, e.g., the cephalic lobe and the preganglionic region are the most susceptible portions of the external surface (Child, '13 b). Moreover, in the fully developed animal differences in the relative susceptibility appear with different agents (Child, '20 b, pp. 157-159). These real or apparent specificities are, however, of secondary origin and are associated with the progress of differentiation. Their existence does not in any way conflict with, or make impossible the existence of the general quantitative relations which determine the susceptibility gradients in the less highly specialized protoplasms.

INHERITANCE AND EXPERIMENTAL REPRODUCTION IN *PLANARIA*

It is sufficiently obvious that at least certain aspects of the problem of inheritance can be approached only through development; that is, knowledge of the hereditary potentialities of a particular protoplasm can be obtained only through the realization of these potentialities in development. Moreover, it is now generally recognized that so-called normal development represents only a certain range of realization among the hereditary potentialities. In other words, normal development is merely the particular complex and sequence of changes which is possible in a particular protoplasm under what we call normal conditions. The relatively high degree of uniformity in normal development results from the fact that it represents a process which is, so to speak, standardized by the relatively high degree of uniformity of the conditions under which it occurs.

When the conditions are altered, the actual behavior of the protoplasmic system is altered and other potentialities than the normal are realized.

As its title indicates, this series of papers has been regarded as a study of inheritance, as well as of development, because the facts of development established afford a basis for certain conclusions concerning inheritance. As regards the head of *Planaria*, for example, it is evident that all the different forms of head are just as truly inherited as the normal; that is, all of them represent potentialities of the physicochemical system which is the material substratum of inheritance. Which of these potentialities is realized depends upon the conditions of development. Or we may say if we wish that under certain external conditions of development a particular head-frequency is inherited for a certain size of piece from a certain body-region of animals of a certain size of physiological age and a certain nutritive condition. This, however, means exactly the same thing as the preceding form of statement.

If we attempt to retain a strictly preformistic conception of inheritance, the facts in the case of *Planaria* force us to the conclusion that a grouping or association of determinants, genes, or factors must exist for each form of head occurring in development, a particular grouping being activated by each particular complex of developmental conditions. But the head-forms constitute a graded series differing primarily in degree and an indefinite number of forms is possible. Any preformistic view which regards these groupings as actually existing in space and time in the germ plasm rather than as mere possibilities of action in a complex physicochemical system, leads either to absurdity or to some form of 'vitalism.'

The point to which I wish to call particular attention, however, is that developmental conditions which differ primarily in a quantitative rather than in a qualitative way may determine qualitative differences in the developmental realization of the hereditary potentialities. In other words, they may determine presence or absence of a particular organ or character. A certain degree of retardation or inhibition of development in *Planaria*

whether produced by low temperature or other external physical or chemical agents or by physiological conditions, will determine complete absence of eyes and of most or all of the ganglionic mass. The series of heads from normal to acephalic is physiologically a series whose terms differ primarily in a quantitative rather than a qualitative way, the qualitative differences which arise resulting from the quantitative differences. The same is true of any other graded series of forms resulting from differential susceptibility; e.g., the sea-urchin modifications (Child, '16 b). *Planaria* does not of course inherit any particular type of head, but merely the potentiality of giving rise under conditions differing in degree or quantity to a graded series of head-forms, with an indefinite number of terms in the series. The hereditary factors, genes, or whatever we prefer to call them which are concerned in head formation in *Planaria*, are unquestionably all present in all forms of head but the sort of head which appears is determined on the one hand by quantitative physiological differences between different regions of the body and on the other by primarily quantitative alteration of these conditions through the non-specific action of physical or chemical factors.

The physiological gradients of the whole body of *Planaria* or of any other axiate form are primarily quantitative, physiological feature, very similar in character in specifically different protoplasms, and such gradients are merely factors in determining the first steps of the process of realization of hereditary potentialities. A physiological gradient is merely a quantitative physiological factor affecting the action of the hereditary mechanism of a specific protoplasm. As pointed out elsewhere, it is the primary pattern of the organism (Child, '20 b). The protoplasm of the species with its hereditary constitution representing a wide range of potentialities is the material in which the pattern is, so to speak, worked out. The pattern, in its simplest terms the physiological gradient, is the organizing factor. The gradient determines localization, order, proportion, and even presence or absence of particular parts, but the specific characteristics of the parts present are determined by the hereditary constitution of the protoplasm.

This quantitative aspect of organization has been emphasized here because it is essential that we distinguish clearly between the specific hereditary mechanism or constitution of each particular protoplasm and the quantitative physiological factor which makes possible the development of a definite and orderly organism from this protoplasm. There has been much confusion on this point, both from the preformistic and the epigenetic view-point, but many different lines of evidence force us to the conclusion that, while the physicochemical constitution of organs or parts depends on the specific constitution of the protoplasm in which they develop, the existence of organization depends primarily upon graded quantitative differences in physiological condition in the protoplasm. Alteration of these quantitative factors determines alteration of the organization within the limits of the particular protoplasm. Under this category fall all the developmental modifications dependent upon differential susceptibility. They represent, in short, alterations of the organizing factor in a specific protoplasm. Such alterations according to the evidence, are initiated as quantitative changes, changes in degree, rate, intensity, rather than changes in kind, but the results, both morphological and physiological, may differ in kind, that is, qualitatively.

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