

animals blastomeres may almost exactly correspond in origin and relative position, yet differ widely in their relation to the resulting embryo. Thus we find that the cleavage of polyclades, annelids, and gasteropods (Fig. 188) shows a really wonderful agreement in form, yet the individual cells differ markedly in prospective value. In all of these forms three quartets of micromeres are successively formed according to exactly the same remarkable law of the alternation of the spirals;<sup>1</sup> and, in all, the posterior cell of a fourth quartet lies at the hinder end of the embryo in precisely the same geometrical relation to the remainder of the embryo; yet in the gasteropods and annelids this cell gives rise to the mesoblast-bands and their products, in the polyclade to a part of the archenteron, while important differences also exist in the value of the other quartets. The relation of the part to the whole is therefore of a highly subtle character, the prospective value of a blastomere depending not merely upon its geometrical position, but upon its relation to the whole complex inherited organization of which it forms a part. The apparently simple conclusion stated in Driesch's clever aphorism thus leads to further problems of the highest complexity. It should be here pointed out that Driesch does not accept Hertwig's theory of the interaction of blastomeres as such, but, like Whitman, Morgan, and others, has brought forward effective arguments against that too simple and mechanical conception. That theory is, in fact, merely Schwann's cell-composite theory of the organism applied to the developing embryo, and the general arguments against that theory find some of their strongest support in the facts of growth and development.<sup>2</sup> This has been forcibly urged by Whitman ('93), who almost simultaneously with the statements of Driesch and Hertwig, cited above, expressed the conviction that the morphogenic process cannot be conceived as merely the sum total or resultant of the individual cell-activities, but operates as a unit without respect to cell-boundaries, precisely as De Bary concludes in the case of growing plant-tissues (p. 393), and the nature of that process is due to the organization of the egg as a whole.

While recognizing fully the great value of the results attained during the past few years in the field of experimental and speculative embryology, we are constrained to admit that as far as the essence of the problem is concerned we have not gone very far beyond the conclusions stated above; for beyond the fact that the inherited organization is involved in that of the germ-cells we remain quite ignorant of its essential nature. This has been recognized by no one more clearly than by Driesch himself, to whose critical researches we owe so much in this field. At the climax of a recent elaborate analysis, the high interest of which is somewhat obscured by

<sup>1</sup> Cf. p. 368.

<sup>2</sup> Cf. pp. 388-394.

its too abstruse form, Driesch can only reiterate his former aphorism,<sup>1</sup> finally taking refuge in an avowed theory of vitalism which assumes the localization of morphogenic phenomena to be determined by "a wholly unknown principle of correlation,"<sup>2</sup> and forms a problem *sui generis*.<sup>3</sup> This conclusion recognizes the fact that the fundamental problem of development remains wholly unsolved, thus confirming from a new point of view a conclusion which it is only fair to point out has been reached by many others.

But while the fundamental nature of the morphogenic process thus remains unknown, we have learned some very interesting facts regarding the conditions under which it takes place, and which show that Driesch's aphorism loses its meaning unless carefully qualified. The experiments referred to at pages 353, 410, show that up to a certain stage of development the blastomeres of the early echinoderm, *Amphioxus* or medusa-embryo, are "totipotent" (Roux), or "equipotential" (Driesch), *i.e.* capable of producing any or all parts of the body. Even in these cases, however, we cannot accept the early conclusion of Pflüger ('83), applied by him to the frog's egg, and afterward accepted by Hertwig, that the material of the egg, or of the blastomeres into which it splits up, is absolutely "isotropic," *i.e.* consists of quite uniform indifferent material, devoid of preëstablished axes. Whitman and Morgan, and Driesch himself, showed that this cannot be the case in the echinoderm egg; for the ovum possesses a polarity predetermined before cleavage begins, as proved by the fact that at the fourth cleavage a group of small cells or micromeres always arises at a certain point, which may be precisely located before cleavage by reference to the eccentricity of the first cleavage-nucleus,<sup>4</sup> and which, as Morgan showed,<sup>5</sup> is indicated before the third, and sometimes before the second cleavage, by a migration of pigment away from the micromere-pole. These observers are thus led to the assumption of a primary polarity of the egg-protoplasm, to which Driesch, in the course of further analysis of the phenomena, is compelled to add the assumption of a secondary polarity at right angles to the first.<sup>6</sup> These polarities, inherent not only in the entire egg, but also in each of the blastomeres into which it divides, form the primary conditions under which the bilaterally symmetrical organism develops by epigenesis. To this extent, therefore, the material of the blastomeres, though "totipotent," shows a certain predetermination with respect to the adult body.

<sup>1</sup> '99, pp. 86-87.

<sup>2</sup> This phrase is cited by Driesch from an earlier work ('92, p. 596) as giving a correct though "unanalytical" statement of his view. It may be questioned whether many readers will regard as an improvement the "analytical" form it assumes in his last work.

<sup>3</sup> *L.c.*, p. 90.

<sup>4</sup> *Cf.* Fig. 103.

<sup>5</sup> '94, p. 142.

<sup>6</sup> See Driesch, '93, pp. 229, 241; '96, and '99, p. 44.

We now proceed to the consideration of experiments which show that in some animal eggs such predetermination may go much farther, so that the development does, in fact, show many of the features of a mosaic-work, as maintained by Roux. The best-determined of these cases is that of the ctenophore-egg, as shown by the work of Chun,

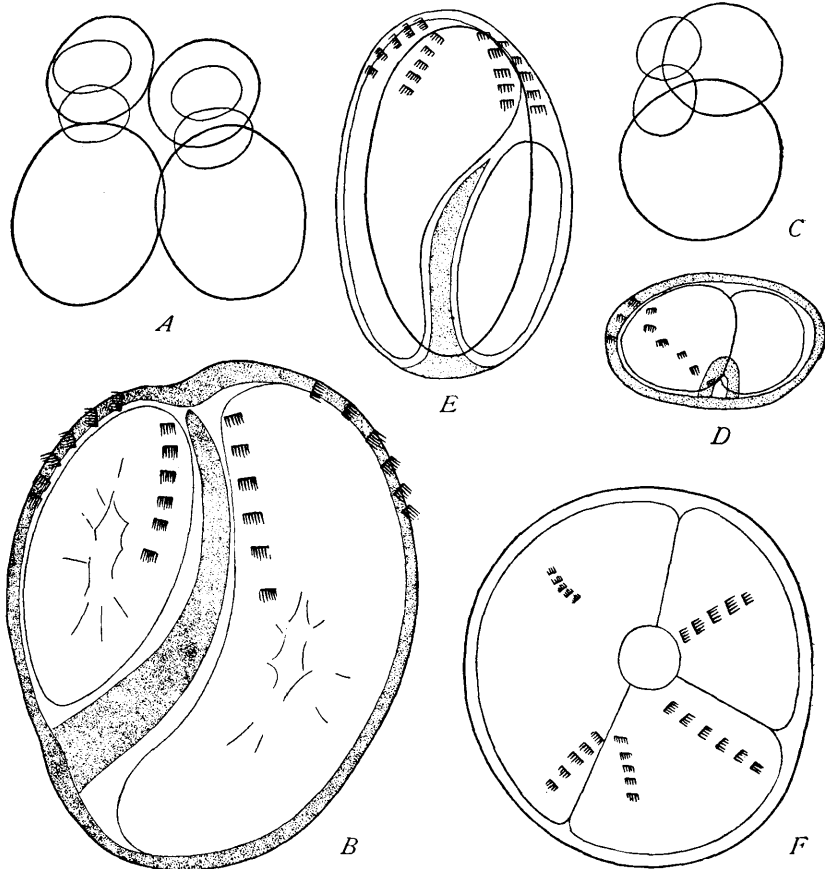


Fig. 189. — Partial larvæ of the ctenophore *Beroë*. [DRIESCH and MORGAN.]

*A.* Half sixteen-cell stage, from an isolated blastomere. *B.* Resulting larva, with four rows of swimming-plates and three gastric pouches. *C.* One-fourth sixteen-cell stage, from an isolated blastomere. *D.* Resulting larva, with two rows of plates and two gastric pouches. *E.* Defective larva, with six rows of plates and three gastric pouches, from a nucleated fragment of an unsegmented egg. *F.* Similar larva with five rows of plates, from above.

Driesch, and Morgan ('95), and Fischel ('98). These observers have demonstrated that isolated blastomeres of the two-, four-, or eight-cell stage undergo a cleavage which, through the earliest stages, is exactly like that which it would have undergone if forming part of a com-

plete embryo, and gives rise to a defective larva, having only four, two, or one row of swimming-plates (Fig. 189); and Fischel's observations give strong reason to believe that each of the eight micromeres of the sixteen-cell stage is definitely specified for the formation of one of the rows of plates. In like manner Crampton ('96) found that in case of the marine gasteropod *Ilyanassa* isolated blastomeres of two-cell or four-cell stages segmented exactly as if forming part of an entire embryo, and gave rise to *fragments* of a larva, not to complete dwarfs, as in the echinoderm (Fig. 190). Further, in embryos from which the "yolk-lobe" (a region of that macromere from which the primary mesoblast normally arises) had been removed, no mesoblast-bands were formed. Most interesting of all, Driesch and Morgan discovered that if a part of the cytoplasm of an *unsegmented* ctenophore-egg were removed, the remainder gave rise to an incomplete larva, showing definite defects (Fig. 189, *E, F*).

In none of these cases is the embryo able to complete itself, though it should be remarked that neither in the ctenophore nor in the snail is the partial embryo identical with a fragment of a whole embryo, since the micromeres finally enclose the macromeres, leaving no surface of fracture. This extreme is, however, connected by a series of forms with such cases as those of *Amphioxus* or the medusa, where the fragment develops nearly or quite as if it were a whole. In the tunicates the researches of Chabry ('87), Driesch ('94), and Crampton ('97) show that an isolated blastomere of the two-cell stage undergoes a typical half-cleavage (Crampton), but finally gives rise to a nearly perfect tadpole larva lacking only one of the asymmetrically placed sense-organs (Driesch). Next in the series may be placed the frog, where, as Roux, Endres, and Walter have shown, a blastomere of the two-cell stage may give rise to a typical half-morula, half-gastrula, and half-embryo<sup>1</sup> (Fig. 182), yet finally produces a perfect larva. A further stage is given by the echinoderm-egg, which, as Driesch showed, undergoes a half-cleavage and produces a half-blastula, which, however, closes to form a whole before the gastrula-stage (Fig. 183). Perfectly formed though dwarf larvæ result. Finally, we reach *Amphioxus* and the hydromasæ in which a perfect "whole development" usually takes place from the beginning, though it is a very interesting fact that the isolated blastomeres of *Amphioxus* sometimes show, in the early stages of cleavage, peculiarities of development that recall their behaviour when forming part of an entire embryo.<sup>2</sup>

We see throughout this series an effort, as it were, on the part of the isolated blastomere to assume the mode of development characteristic of a complete egg, but one that is striving against conditions that

<sup>1</sup> This is not invariably the case, as described beyond.

<sup>2</sup> Cf. Wilson, '93, pp. 590, 608.

tend to confine its operations to the rôle it would have played if still forming part of an entire developing egg. In *Amphioxus* or *Clytia* this tendency is successful almost from the beginning. In other forms the limiting conditions are only overcome at a later period, while in the ctenophore or snail they seem to afford an insurmount-

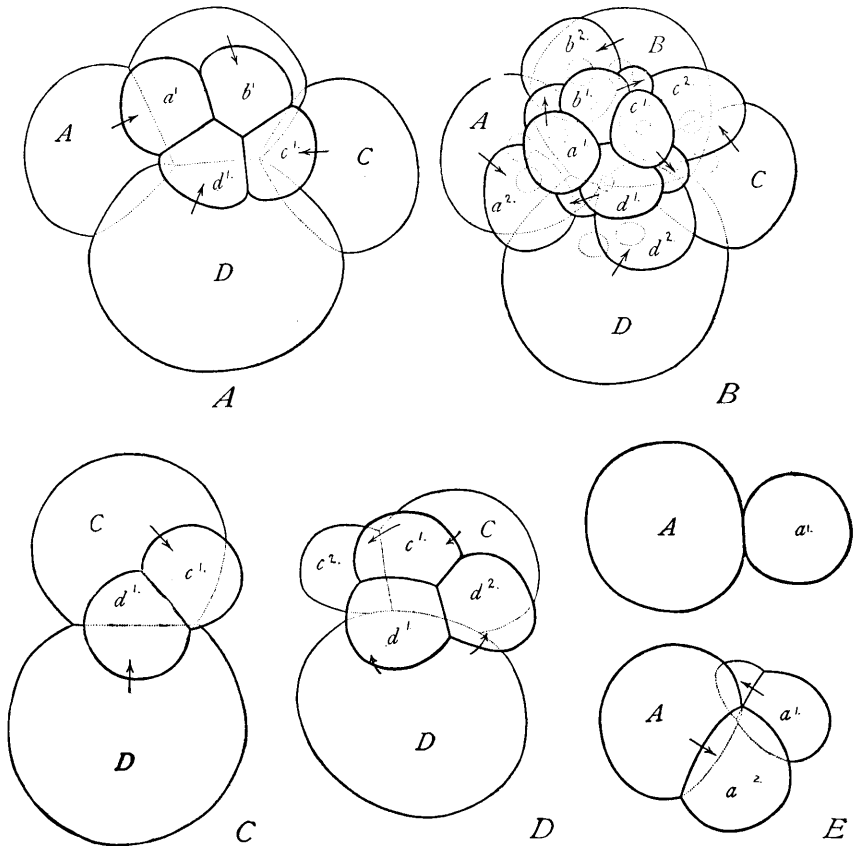


Fig. 190. — Partial development of isolated blastomeres of the gasteropod egg, *Ilyanassa*. [CRAMPTON.]

A. Normal eight-cell stage. B. Normal sixteen-cell stage. C. Half eight-cell stage, from isolated blastomere of the two-cell stage. D. Half twelve-cell stage succeeding. E. Two stages in the cleavage of an isolated blastomere of the four-cell stage; above a one-fourth eight-cell stage, below a one-fourth sixteen-cell stage.

able barrier to complete development. What determines the limitations of development in these various cases? They cannot be due to nuclear specification; for in the ctenophore the fragment of an *unsegmented* egg, containing the normal egg-nucleus, gives rise to a defective larva; and my experiments on *Nereis* show that even in a highly

determinate cleavage, essentially like that of the snail, the nuclei may be shifted about by pressure without altering the end-result. Neither can they lie in the form of the dividing mass as some authors have assumed; for in Crampton's experiments the half or quarter blastomere does not retain the form of a half or quarter sphere, but rounds

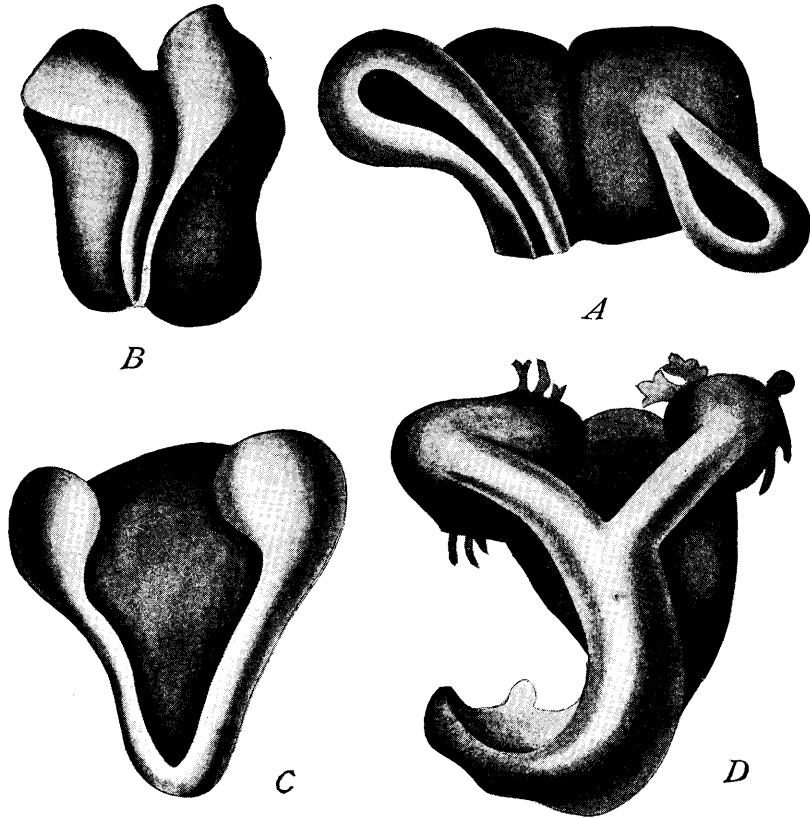


Fig. 191. — Double embryos of frog developed from eggs inverted when in the two-cell stage. [O. SCHULTZE.]

A. Twins with heads turned in opposite directions. B. Twins united back to back. C. Twins united by their ventral sides. D. Double-headed tadpole.

off to a spheroid like the egg. But if the limiting conditions lie neither in the nucleus nor in the form of the mass, we must seek them in the *cytoplasm*; and if we find here factors by which the tendency of the part to develop into a whole may be, as it were, hemmed in, we shall reach a proximate explanation of the mosaic-like character of cleavage shown in the forms under consideration, and the mosaic

theory of cytoplasmic localization will find a substantial if somewhat restricted basis.

That we are here approaching the true explanation is indicated by certain very remarkable and interesting experiments on the frog's egg, which prove that each of the first two blastomeres may give rise either to a half-embryo or to a whole embryo of half size, according to circumstances, and which indicate, furthermore, that these circumstances lie in a measure in the arrangement of the cytoplasmic materials. This most important result, which we owe especially to Morgan,<sup>1</sup> was reached in the following manner. Born had shown, in 1885, that if frogs' eggs be fastened in an abnormal position, — *e.g.* upside down, or on the side, — a rearrangement of the egg-material takes place, the heavier deutoplasm sinking toward the lower side, while the nucleus and protoplasm rise. *A new axis is thus established in the egg*, which has the same relation to the body-axes as in the ordinary development (though the pigment retains its original arrangement). This proves that in eggs of this character (telolecithal) the distribution of deutoplasm, or conversely of protoplasm, is one of the primary formative conditions of the cytoplasm; and the significant fact is that *by artificially changing this distribution the axis of the embryo is shifted*. Oscar Schultze ('94) discovered that if the egg be turned upside down when in the two-cell stage, a whole embryo (or half of a double embryo) may arise from each blastomere instead of a half-embryo as in the normal development, and that the axes of these embryos show no constant relation to one another (Fig. 191). Morgan ('95, 3) added the important discovery that either a half-embryo or a whole half-sized dwarf might be formed, *according to the position of the blastomere*. If, after destruction of one blastomere, the other be allowed to remain in its normal position, a half-embryo always results,<sup>2</sup> precisely as described by Roux. If, on the other hand, the blastomere be inverted, it may give rise either to a half-embryo<sup>3</sup> or to a whole dwarf.<sup>4</sup> Morgan therefore concluded that the production of whole embryos by the inverted blastomeres was, in part at least, due to a rearrangement or rotation of the egg-materials under the influence of gravity, the blastomere thus returning, as it were, to a state of equilibrium like that of an entire ovum.

This beautiful experiment gives most conclusive evidence that each of the two blastomeres contains all the materials, nuclear and cytoplasmic, necessary for the formation of a whole body; and that these materials may be used to build a whole body or half-body, according to the grouping that they assume. After the first cleavage takes

<sup>1</sup> *Anat. Anz.*, X, 19, 1895.

<sup>2</sup> Eleven cases observed.

<sup>3</sup> Three cases.

<sup>4</sup> Nine cases observed.

place, each blastomere is *set*, as it were, for a half-development, but not so firmly that a rearrangement is excluded.

I have reached a nearly related result in the case of both *Amphioxus* and the echinoderms. In *Amphioxus* the isolated blastomere usually segments like an entire ovum of diminished size. This is, however, not invariable, for a certain number of such blastomeres show a more or less marked tendency to divide as if still forming part of an entire embryo. The sea-urchin *Toxopneustes* reverses this rule, for the isolated blastomere of the two-cell stage usually shows a perfectly typical half-cleavage, as described by Driesch, but in rare cases it may segment like an *entire* ovum of half-size (Fig. 183, *D*) and give rise to an entire blastula. We may interpret this to mean that in *Amphioxus* the differentiation of the cytoplasmic substance is at first very slight, or readily alterable, so that the isolated blastomere, as a rule, reverts at once to the condition of the entire ovum. In the sea-urchin, the initial differentiations are more extensive or more firmly established, so that only exceptionally can they be altered. In the snail and ctenophore we have the opposite extreme to *Amphioxus*, the cytoplasmic conditions having been so firmly established that they cannot be readjusted, and the development must, from the outset, proceed within the limits thus set up.

Through this conclusion we reconcile, as I believe, the theories of cytoplasmic localization and mosaic development with the hypothesis of cytoplasmic totipotence. Primarily the egg-cytoplasm is totipotent in the sense that its various regions stand in no fixed relation with the parts to which they respectively give rise, and the substance of each of the blastomeres into which it splits up contains all of the materials necessary to the formation of a complete body. Secondly, however, development may assume more or less of a mosaic-like character through differentiations of the cytoplasmic substance involving local chemical and physical changes, deposits of metaplastic material, and doubtless many other unknown subtler processes. Both the extent and the rate of such differentiations seem to vary in different cases; and here probably lies the explanation of the fact that the isolated blastomeres of different eggs vary so widely in their mode of development. When the initial differentiation is of small extent or is of such a kind as to be readily modified, cleavage is *indeterminate* in character and may easily be remodelled (as in *Amphioxus*). When they are more extensive or more rigid, cleavage assumes a mosaic-like or *determinate* character,<sup>1</sup> and qualitative division, in a certain sense, becomes a fact. Conklin's ('99) interesting observations on the highly determinate cleavage of gasteropods (*Crepidula*)

<sup>1</sup> The convenient terms *indeterminate* and *determinate* cleavage were suggested by Conklin ('98).



show that here the substance of the attraction-spheres is unequally distributed, in a quite definite way, among the cleavage-cells, each sphere of a daughter-cell being carried over bodily into one of the granddaughter-cells (Fig. 192). We have here a substantial basis for the conclusion that in cleavage of this type qualitative division of the cytoplasm may occur.

It is important not to lose sight of the fact that development and differentiation do not in any proper sense first begin with the cleavage of the ovum, but long before this, during its ovarian history.<sup>1</sup> The primary differentiations thus established in the cytoplasm form the immediate conditions to which the later development must conform; and the difference between *Amphioxus* on the one hand, and the

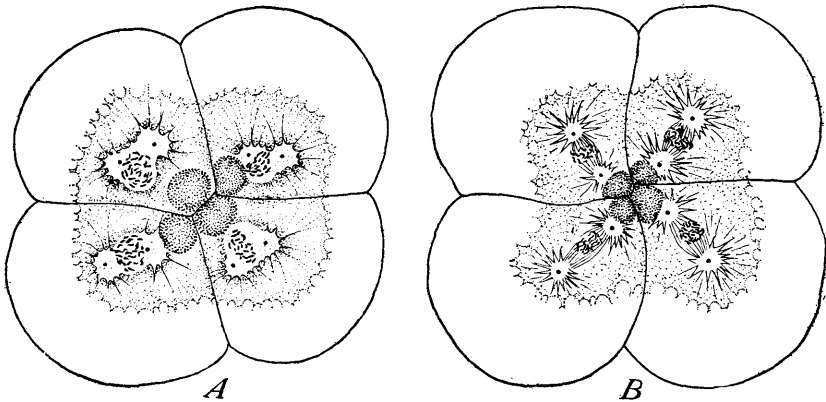


Fig. 192. — Two successive stages in the third cleavage of the egg of *Crepidula*, seen from the upper pole. [CONKLIN.]

In both figures the old spheres (dotted) lie at the upper pole of the embryo, and at the third cleavage they pass into the four respective cells of the first quartet of micromeres. The centrosomes are seen in the new spheres.

snail or ctenophore on the other, simply means, I think, that the initial differentiation is less extensive or less firmly established in the one than in the other.

The origin of the cytoplasmic differentiations existing at the beginning of cleavage has already been considered (p. 386). If the conclusions there reached be placed beside the above, we reach the following conception. The primary determining cause of development lies in the nucleus, which operates by setting up a continuous series of specific metabolic changes in the cytoplasm. This process begins during ovarian growth, establishing the external form of the egg, its primary polarity, and the distribution of substances within it. The cytoplasmic differentiations thus set up form as it were a frame-

<sup>1</sup> See Wilson ('96), Driesch ('98, 1).

work within which the subsequent operations take place in a course which is more or less firmly fixed in different cases. If the cytoplasmic conditions be artificially altered by isolation or other disturbance of the blastomeres, a readjustment may take place and development may be correspondingly altered. Whether such a readjustment is possible depends on secondary factors—the extent of the primary differentiations, the physical consistency of the egg-substance, the susceptibility of the protoplasm to injury, and doubtless a multitude of others. The same doubtless applies to the later stages of development; and we must here seek for some of the factors by which the power of regeneration in the adult is determined and limited. It is, however, not improbable, as pointed out below, that in the later stages differentiation may occur in the nuclear as well as in the cytoplasmic substance.

#### G. THE NUCLEUS IN LATER DEVELOPMENT

The foregoing conception, as far as it goes, gives at least an intelligible view of the more general features of early development and in a measure harmonizes the apparently conflicting results of experiment on various forms. But there are a very large number of facts relating especially to the later stages of differentiation, which it seems to leave unexplained, and which indicate that the nucleus as well as the cytoplasm may undergo progressive changes of its substance. It has been assumed by most critics of the Roux-Weismann theory that all of the nuclei of the body contain the same idioplasm, and that each therefore, in Hertwig's words, contains the germ of the whole. It is, however, doubtful whether this assumption is well founded. The power of a single cell to produce the entire body is in general limited to the earliest stages of cleavage, rapidly diminishes, and as a rule soon disappears entirely. When once the germ-layers have been definitely separated, they lose entirely the power to regenerate one another save in a few exceptional cases. In asexual reproduction, in the regeneration of lost parts, in the formation of morbid growths, each tissue is in general able to reproduce only a tissue of its own or a nearly related kind. Transplanted or transposed groups of cells (grafts and the like) retain more or less completely their autonomy and vary only within certain well-defined limits, despite their change of environment. All of these statements are, it is true, subject to exception; yet the facts afford an overwhelming demonstration that differentiated cells possess a specific character, that their power of development and adaptability to changed conditions becomes in a greater or less degree limited with the progress of development. As indicated above, this progressive specification of the tissue-cells

is no doubt due in part to differentiation of the cytoplasm. There is, however, reason to suspect that, beyond this, *differentiation may sooner or later involve a specification of the nuclear substance*. When we reflect on the general rôle of the nucleus in metabolism and its significance as the especial seat of the formative power, we may well hesitate to deny that this part of Roux's conception may be better founded than his critics have admitted. Nägeli insisted that the idioplasm must undergo a progressive transformation during development, and many subsequent writers, including such acute thinkers as Boveri and Nussbaum, and many pathologists, have recognized the necessity for such an assumption. Boveri's remarkable observations on the nuclei of the primordial germ-cells in *Ascaris* demonstrate the truth of this view in a particular case; for here *all of the somatic nuclei lose a portion of their chromatin, and only the progenitors of the germ-nuclei retain the entire ancestral heritage*. Boveri himself has in a measure pointed out the significance of his discovery, insisting that the specific development of the tissue-cells is conditioned by specific changes in the chromatin that they receive,<sup>1</sup> though he is careful not to commit himself to any definite theory. It hardly seems possible to doubt that in *Ascaris* the limitation of the somatic cells in respect to the power of development arises through a loss of particular portions of the chromatin. One cannot avoid the thought that further and more specific limitations in the various forms of somatic cells may arise through an analogous process, and that we have here a key to the origin of nuclear specification *without recourse to the theory of qualitative division*. We do not need to assume that the unused chromatin is cast out bodily; for it may degenerate and dissolve, or may be transformed into linin-substance or into nucleoli.

This suggestion is made only as a tentative hypothesis, but the phenomena of mitosis seem well worthy of consideration from this point of view. Its application to the facts of development becomes clearer when we consider the nature of the nuclear "control" of the cell, *i.e.* the action of the nucleus upon the cytoplasm. Strasburger, following in a measure the lines laid down by Nägeli, regards the action as essentially dynamic, *i.e.* as a propagation of molecular movements from nucleus to cytoplasm in a manner which might be compared to the transmission of a nervous impulse. When, however, we consider the rôle of the nucleus in synthetic metabolism, and the relation between this process and that of morphological synthesis, we must regard the question in another light; and opinion has of late strongly tended to the conclusion that nuclear "control" can only be explained as the result of active exchanges of material between nucleus and cytoplasm. De Vries, followed by Hertwig,

<sup>1</sup> '91, p. 433.

assumes a migration of pangens from nucleus to cytoplasm, the character of the cell being determined by the nature of the migrating pangens, and these being, as it were, selected by circumstances (position of the cell, etc.). But, as already pointed out, the pangen-hypothesis should be held quite distinct from the purely physiological aspect of the question, and may be temporarily set aside; for specific nuclear substances may pass from the nucleus into the cytoplasm in an unorganized form. Sachs, followed by Loeb, has advanced the hypothesis that the development of particular organs is determined by specific "formative substances" which incite corresponding forms of metabolic activity, growth, and differentiation. It is but a step from this to the very interesting suggestion of Driesch that the nucleus is a storehouse of ferments which pass out into the cytoplasm and there set up specific activities. Under the influence of these ferments the cytoplasmic organization is determined at every step of the development, and new conditions are established for the ensuing change. This view is put forward only tentatively as a "fiction" or working hypothesis; but it is certainly full of suggestion. Could we establish the fact that the number of ferments or formative substances in the nucleus diminishes with the progress of differentiation, we should have a comparatively simple and intelligible explanation of the specification of nuclei and the limitation of development. The power of regeneration might then be conceived, somewhat as in the Roux-Weismann theory, as due to a retention of idioplasm or germ-plasm — *i.e.* chromatin — in a less highly modified condition, and the differences between the various tissues in this regard, or between related organisms, would find a natural explanation.

Development may thus be conceived as a progressive transformation of the egg-substance primarily incited by the nucleus, first manifesting itself by specific changes in the cytoplasm, but sooner or later involving in some measure the nuclear substance itself. This process, which one is tempted to compare to a complicated and progressive form of crystallization, begins with the youngest ovarian egg and proceeds continuously until the cycle of individual life has run its course. Cell-division is an accompaniment but not a direct cause of differentiation. The cell is no more than a particular area of the germinal substance comprising a certain quantity of cytoplasm and a mass of idioplasm in its nucleus. Its character is primarily a manifestation of the general formative energy acting at a particular point under given conditions. When once such a circumscribed area has been established, it may, however, emancipate itself in a greater or less degree from the remainder of the mass, and acquire a specific character so fixed as to be incapable of further change save within the limits imposed by its acquired character.

## H. THE EXTERNAL CONDITIONS OF DEVELOPMENT

We have thus far considered only the internal conditions of development which are progressively created by the germ-cell itself. We must now briefly glance at the external conditions afforded by the environment of the embryo. That development is conditioned by the external environment is obvious. But we have only recently

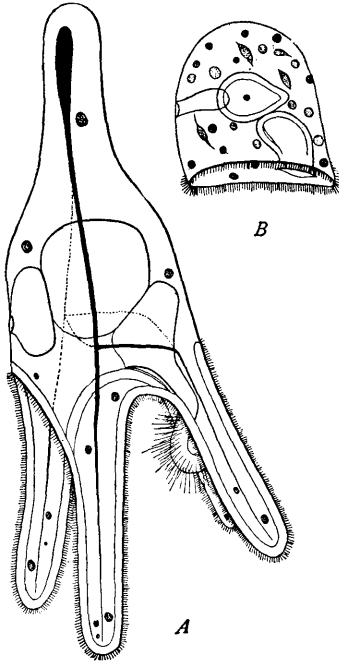


Fig. 193.— Normal and modified larvæ of sea-urchins. [HERBST.]

A. Normal Pluteus (*Strongylocentrotus*). B. Larva (*Sphaerechinus*) at the same stage as the foregoing, developed in sea-water containing a slight excess of potassium chloride.

come to realize how intimate the relation is; and it has been especially the service of Loeb, Herbst, and Driesch to show how essential a part is played by the environment in the development of specific organic forms. The limits of this work will not admit of any adequate review of the vast array of known facts in this field, for which the reader is referred to the works especially of Herbst. I shall only consider one or two cases which may serve to bring out the general principle that they involve. Every living organism at every stage of its existence reacts to its environment by physiological and morphological changes. The developing embryo, like the adult, is a moving equilibrium — a product of the response of the inherited organization to the external stimuli working upon it. If these stimuli be altered, development is altered. This is beautifully shown by the experiments of Herbst and others on the development of sea-urchins. Pouchet and Chabry showed that if the embryos of these animals be made to develop in sea-water containing no lime-salts, the larva fails to develop not only its calcareous skeleton, but also its ciliated arms, and a larva thus results that resembles in some particulars an entirely different specific form; namely, the *Tornaria* larva of *Balanoglossus*. This result is not due simply to the lack of necessary material; for Herbst showed that the same result is attained if a slight excess of potassium chloride be added to sea-water containing the normal amount of lime (Fig. 193). In the latter case the specific metabolism of the protoplasm is altered by a particular chemical stimulus, and a new form results.

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The changes thus caused by slight chemical alterations in the water may be still more profound. Herbst ('92) observed, for example, that when the water contains a very small percentage of lithium chloride, the blastula of sea-urchins fails to invaginate to form a typical gastrula, but *evaginates* to form an hour-glass-shaped

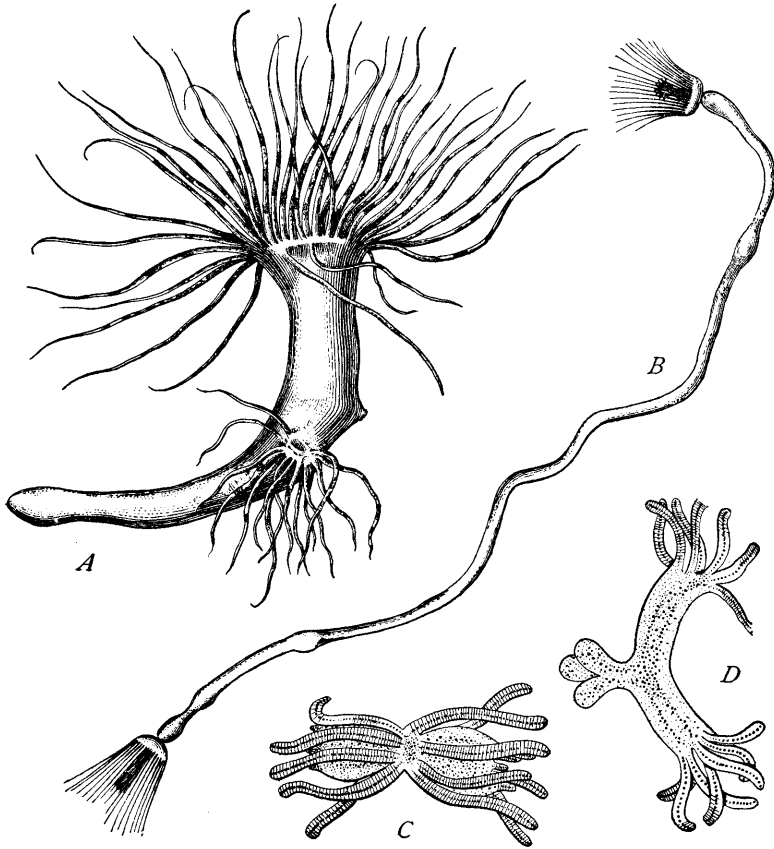


Fig. 194.—Regeneration in coelenterates (A, B, from LOEB; C, D, from BICKFORD).

A. Polyp (*Cerianthus*), producing new tentacles from the *aboral* side of a lateral wound. B. Hydroid (*Tubularia*), generating a head at each end of a fragment of the stem suspended in water. C, D. Similar generation of heads at both ends of short pieces of the stem, in *Tubularia*.

larva, one half of which represents the archenteron, the other half the ectoblast. Moreover, a much larger number of the blastula-cells undergo the differentiation into entoblast than in the normal development, the ectoblast sometimes becoming greatly reduced and occasionally disappearing altogether, so that the entire blastula is

differentiated into cells having the histological character of the normal entoblast! One of the most fundamental of embryonic differentiations is thus shown to be intimately conditioned by the chemical environment.

The observations of botanists on the production of roots and other structures as the result of local stimuli are familiar to all. Loeb's interesting experiments on hydroids give a similar result ('91). It has long been known that *Tubularia*, like many other hydroids, has the power to regenerate its "head" — *i.e.* hypostome, mouth, and tentacles — after decapitation. Loeb proved that in this case the power to form a new head is conditioned by the environment. For if a *Tubularia* stem be cut off at both ends and inserted in the sand upside down, *i.e.* with the oral end buried, a new head is regenerated at the free (formerly aboral) end. Moreover, if such a piece be suspended in the water by its middle point, a new head is produced at *each end* (Fig. 194); while if both ends be buried in the sand, neither end regenerates. This proves in the clearest manner that in this case the power to form a definite complicated structure is called forth by the stimulus of the external environment.

These cases must suffice for our purpose. They prove incontestably that *normal development is in a greater or less degree the response of the developing organism to normal conditions*; and they show that we cannot hope to solve the problems of development without reckoning with these conditions. But neither can we regard specific forms of development as *directly caused* by the external conditions; for the egg of a fish and that of a polyp develop, side by side, in the same drop of water, under identical conditions, each into its predestined form. Every step of development is a physiological reaction, involving a long and complex chain of cause and effect between the stimulus and the response. The character of the response is determined, not by the stimulus, but by the *inherited organization*. While, therefore, the study of the external conditions is essential to the analysis of embryological phenomena, it serves only to reveal the mode of action of the germ and gives but a dim insight into its ultimate nature.

## I. DEVELOPMENT, INHERITANCE, AND METABOLISM

In bringing the foregoing discussion into more direct relation with the general theory of cell-action, we may recall that the cell-nucleus appears to us in two apparently different *rôles*. On the one hand, it is a primary factor in morphological synthesis and hence in inheritance, on the other hand an organ of metabolism especially concerned with the constructive process. These two functions we may with

Claude Bernard regard as but different phases of one process. The building of a definite cell-product, such as a muscle-fibre, a nerve-process, a cilium, a pigment-granule, a zymogen-granule, is in the last analysis the result of a specific form of metabolic activity, as we may conclude from the fact that such products have not only a definite physical and morphological character, but also a definite chemical character. In its physiological aspect, therefore, inheritance is the recurrence, in successive generations, of like forms of metabolism; and this is effected through the transmission from generation to generation of a specific substance or idioplasm which we have seen reason to identify with chromatin. The validity of this conception is not affected by the form in which we conceive the morphological nature of the idioplasm—whether as simply a mixture of chemical substances, as a microcosm of invisible germs or pangens, as assumed by De Vries, Weismann, and Hertwig, as a storehouse of specific ferments as Driesch suggests, or as a complex molecular substance grouped in micellæ as in Nägeli's hypothesis. It is true, as Verworn insists, that the cytoplasm is essential to inheritance; for without a specifically organized cytoplasm the nucleus is unable to set up specific forms of synthesis. This objection, which has already been considered from different points of view, by both De Vries and Driesch, disappears as soon as we regard the egg-cytoplasm as *itself a product of the nuclear activity*; and it is just here that the general rôle of the nucleus in metabolism is of such vital importance to the theory of inheritance. If the nucleus be the formative centre of the cell, if nutritive substances be elaborated by or under the influence of the nucleus while they are built into the living fabric, then the specific character of the cytoplasm is determined by that of the nucleus, and the contradiction vanishes. In accepting this view we admit that the cytoplasm of the egg is, in a measure, the substratum of inheritance, but it is so only by virtue of its relation to the nucleus, which is, so to speak, the ultimate court of appeal. The nucleus cannot operate without a cytoplasmic field in which its peculiar powers may come into play; but this field is created and moulded by itself.

#### J. PREFORMATION AND EPIGENESIS. THE UNKNOWN FACTOR IN DEVELOPMENT

We have now arrived at the farthest outposts of cell-research, and here we find ourselves confronted with the same unsolved problems before which the investigators of evolution have made a halt. For we must now inquire what is the guiding principle of embryological development that correlates its complex phenomena and directs them



to a definite end. However we conceive the special mechanism of development, we cannot escape the conclusion that the power behind it is involved in the structure of the germ-plasm inherited from foregoing generations. What is the nature of this structure and how has it been acquired? To the first of these questions we have as yet no certain answer. The second question is merely the general problem of evolution stated from the standpoint of the cell-theory. The first question raises once more the old puzzle of preformation or epigenesis. The pangen-hypothesis of De Vries and Weismann recognizes the fact that development is epigenetic in its external features; but like Darwin's hypothesis of pangensis, it is at bottom a theory of preformation, and Weismann expresses the conviction that an epigenetic development is an impossibility.<sup>1</sup> He thus explicitly adopts the view, long since suggested by Huxley, that "the process which in its superficial aspect is epigenesis appears in essence to be evolution in the modified sense adopted in Bonnet's later writings; and development is merely the expansion of a potential organism or 'original preformation' according to fixed laws."<sup>2</sup> Hertwig ('92, 2), while accepting the pangen-hypothesis, endeavours to take a middle ground between preformation and epigenesis, by assuming that the pangens (idioblasts) represent only *cell-characters*, the traits of the multicellular body arising epigenetically by permutations and combinations of these characters. This conception certainly tends to simplify our ideas of development in its outward features, but it does not explain why cells of different characters should be combined in a definite manner, and hence does not reach the ultimate problem of inheritance.

What lies beyond our reach at present, as Driesch has very ably urged, is to explain the orderly rhythm of development—the coordinating power that guides development to its predestined end. We are logically compelled to refer this power to the inherent organization of the germ, but we neither know nor can we even conceive what that organization is. The theory of Roux and Weismann demands for the orderly distribution of the elements of the germ-plasm a prearranged system of forces of absolutely inconceivable complexity. Hertwig's and De Vries's theory, though apparently simpler, makes no less a demand; for how are we to conceive the power which guides the countless hosts of migrating pangens throughout all the long and complex events of development? The same difficulty confronts us under any theory we can frame. If with Herbert Spencer we assume the germ-plasm to be an aggregation of like units, molecular or supra-molecular, endowed with predetermined polarities which lead to their grouping in specific forms,

<sup>1</sup> *Germ-plasm*, p. 14.

<sup>2</sup> *Evolution, Science, and Culture*, p. 296.

we but throw the problem one stage farther back, and, as Weismann himself has pointed out,<sup>1</sup> substitute for one difficulty another of exactly the same kind.

The truth is that an explanation of development is at present beyond our reach. The controversy between preformation and epigenesis has now arrived at a stage where it has little meaning apart from the general problem of physical causality. What we know is that a specific kind of living substance, derived from the parent, tends to run through a specific cycle of changes during which it transforms itself into a body like that of which it formed a part; and we are able to study with greater or less precision the mechanism by which that transformation is effected and the conditions under which it takes place. But despite all our theories we no more know how the organization of the germ-cell involves the properties of the adult body than we know how the properties of hydrogen and oxygen involve those of water. So long as the chemist and physicist are unable to solve so simple a problem of physical causality as this, the embryologist may well be content to reserve his judgment on a problem a hundred-fold more complex.

The second question, regarding the historical origin of the idioplasm, brings us to the side of the evolutionists. The idioplasm of every species has been derived, as we must believe, by the modification of a preëxisting idioplasm through variation, and the survival of the fittest. Whether these variations first arise in the idioplasm of the germ-cells, as Weismann maintains, or whether they may arise in the body-cells and then be reflected back upon the idioplasm, is a question to which the study of the cell has thus far given no certain answer. Whatever position we take on this question, the same difficulty is encountered; namely, the origin of that coördinated *fitness*, that power of active adjustment between internal and external relations, which, as so many eminent biological thinkers have insisted, overshadows every manifestation of life. The nature and origin of this power is the fundamental problem of biology. When, after removing the lens of the eye in the larval salamander, we see it restored in perfect and typical form by regeneration from the posterior layer of the iris,<sup>2</sup> we behold an adaptive response to changed conditions of which the organism can have had no antecedent experience either ontogenetic or phylogenetic, and one of so marvellous a character that we are made to realize, as by a flash of light, how far we still are from a solution of this problem. It may be true, as Schwann himself urged, that the adaptive power of living beings differs in degree only, not in kind, from that of unor-

<sup>1</sup> *Germinal Selection*, January, 1896, p. 284.

<sup>2</sup> See Wolff, '95, and Müller, '96.

ganized bodies. It is true that we may trace in organic nature long and finely graduated series leading upward from the lower to the higher forms, and we must believe that the wonderful adaptive manifestations of the more complex forms have been derived from simpler conditions through the progressive operation of natural causes. But when all these admissions are made, and when the conserving action of natural selection is in the fullest degree recognized, we cannot close our eyes to two facts: first, that we are utterly ignorant of the manner in which the idioplasm of the germ-cell can so respond to the influence of the environment as to call forth an adaptive variation; and second, that the study of the cell has on the whole seemed to widen rather than to narrow the enormous gap that separates even the lowest forms of life from the inorganic world.

I am well aware that to many such a conclusion may appear reactionary or even to involve a renunciation of what has been regarded as the ultimate aim of biology. In reply to such a criticism I can only express my conviction that the magnitude of the problem of development, whether ontogenetic or phylogenetic, has been underestimated; and that the progress of science is retarded rather than advanced by a premature attack upon its ultimate problems. Yet the splendid achievements of cell-research in the past twenty years stand as the promise of its possibilities for the future, and we need set no limit to its advance. To Schleiden and Schwann the present standpoint of the cell-theory might well have seemed unattainable. We cannot foretell its future triumphs, nor can we doubt that the way has already been opened to better understanding of inheritance and development.

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