eggs under *pressure*. Ordinarily in the sixteen-cell stage of an echinoderm egg the cells are separated by alternate vertical and horizontal planes. Driesch found that if the fertilized egg were compressed between glass plates

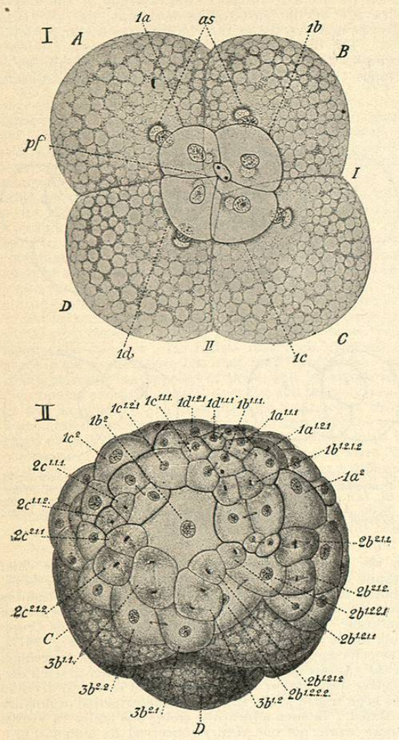

FIG. 2617.—Two Stages Illustrating the Mosaic-like Cleavage of a Mollusc, Crepidula. *I.*, Eight-cell stage; *II.*, stage with one hundred and nine cells. Highly magnified. (After Conklin.)

cleavage would take place, but all the planes would be vertical, so that at the end of the sixteen-cell stage the embryo would consist of a one-layered plate of cells. Relations of the nuclei in such an embryo would be very different from the normal, yet if the pressure were now released the embryo would develop into a perfect larva.

Hertwig obtained the same results from experiments on frogs' eggs. These are of more interest because of the early differentiation of the egg into micromeres and macromeres. Hertwig obtained a different mode of cleavage, according as he compressed the eggs between horizontal or vertical plates, and both of these forms were found to differ very greatly from the normal, cells becoming macromeres which should normally be micromeres and *vice versa*. Yet upon pressure being removed, all developed into normal embryos.

The most interesting experiments in this line are a few performed by E. B. Wilson on fertilized eggs of Nereis (Fig. 2618). They are especially interesting because of the great definiteness of the cleavage in Nereis and because of the results that Crampton obtained from the isolation of the blastomeres of Ilyanassa. Under pressure beneath a cover-glass, the eggs would divide, each forming a flat plate consisting of a single layer of eight cells. "If they are now released from the pressure, each of the cells divides in a plane approximately horizontal, a smaller granular micromere being formed above, leaving below a larger clear macromere in which the oil drops remain. The sixteen-cell stage, therefore, consists of eight deutoplasm-laden macromeres and eight protoplasmic micromeres (instead of four macromeres and twelve micromeres, as in the usual development). These embryos developed into free-swimming trochophores containing eight instead of four macromeres, which have the typical clear protoplasm containing oil drops. In this case there can be no doubt whatever that four of the entroblastic nuclei were normally destined for the first quartet of micromeres (ectoblast) from which arise the apical ganglia and prototroch. Under the conditions of the experiment, however, they have given rise to the nuclei of cells which differ in no wise from the other endoderm cells. The immediate cause of differentiation must therefore be sought not in the distribution of the nuclei or their mode of division, but in the conditions existing in the cytoplasm."

This conclusion is borne out by the converse experiments performed by Morgan upon the egg of Fundulus. In this minnow, as in other fishes, the blastoderm in the

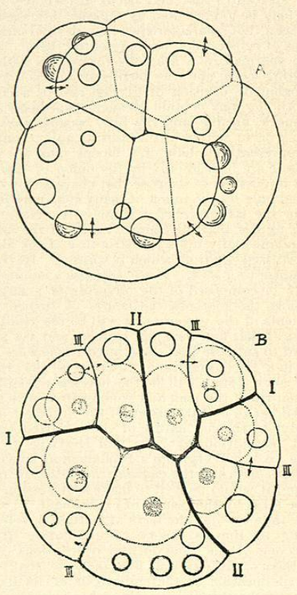

FIG. 2618.—Eight-cell Stage of Nereis. *A*, Normal; *B*, under pressure. Dotted lines show the outlines of the micromeres formed after release from pressure. (After Wilson.)

eight-cell stage consists of a single layer of cells lying on one side of the yolk. Morgan discovered that by pricking a fertilized egg so that part of the yolk escaped, he could apparently reduce the pressure on the germinal disc, which would become rounded and would divide so

that the eight-cell stage consisted of a clump of cells separated by two vertical and one horizontal planes. But in spite of this abnormal cleavage a normal embryo was produced.

The results of the *isolation* of blastomeres are complicated. On the one hand we have experiments like Crampton's, where an isolated blastomere of the two-cell stage continues to develop into a half embryo, as if the other half were present; while, on the other hand, we have the experiments of Zoja, who found that isolated blastomeres of the medusæ, Clytia and Laodice, in the sixteen-cell stage would develop into free swimming larvæ which could not be distinguished, except for their small size, from larvæ developed from whole eggs. (Apparently, however, a one-fourth egg of Clytia was the smallest that would develop into a complete medusa.) Between these two extremes there are species presenting intermediate grades in their capacity to develop from isolated blastomeres. So far as we know now, the form that comes nearest to the medusæ described by Zoja in power to develop from isolated blastomeres is Amphioxus. Wilson discovered that blastomeres of the two-cell stage isolated by shaking would develop precisely like whole eggs, giving rise to perfect blastulas, perfect gastrulas, and nearly perfect larvæ one-half the normal size. The same result was obtained from groups of two blastomeres of the four-cell stage. Single blastomeres of this stage, however, might give rise to perfect blastulas and gastrulas, but the larvæ were less perfect. While from the eight-cell stage single blastomeres would produce only imperfect blastulas, most of them developing as if still part of a whole embryo. Morgan found that if one blastomere of the two-cell stage of Fundulus were killed, the other would develop into a perfect embryo two-thirds of the normal size.

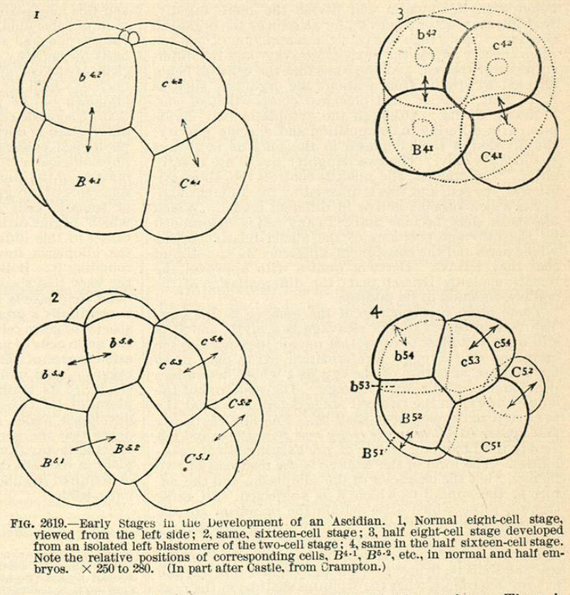

FIG. 2619.—Early Stages in the Development of an Ascidian. 1, Normal eight-cell stage, viewed from the left side; 2, same, sixteen-cell stage; 3, half eight-cell stage developed from an isolated left blastomere of the two-cell stage; 4, same in the half sixteen-cell stage. Note the relative positions of corresponding cells, $B^{4.1}$, $B^{4.2}$, etc., in normal and half embryos. × 250 to 280. (In part after Castle, from Crampton.)

An isolated blastomere of the sea-urchin, Echinus, according to Driesch, develops at first as if it were a half of a whole embryo producing a half blastula. Then the opening closes forming a complete blastula which develops into a gastrula and pluteus. Crampton obtained similar results with eggs of an Ascidian (Fig. 2619).

In the ctenophore, Beroe, we have, as Driesch and Morgan have shown, a condition similar to that found in the gasteropod. Isolated blastomeres of the two- or of the four-cell stage segment as if forming a half or a quarter of a whole embryo, and they give rise finally to imperfect larvæ. Driesch and Morgan made also the interesting discovery that if a fertilized ctenophore egg have part of the cytoplasm removed, it also gives rise to an imperfect larva "showing certain defects which represent the parts removed." This last observation shows that the cytoplasm may be of importance in directing development. For here a defect in the cytoplasm gives rise to a definite deformity in the larva.

All of these results, taken together, make a very strong case against the theory of qualitative divisions. The isolation experiments show that in many cases a nucleus which normally should give rise to nuclei of only one-sixteenth, one-eighth, one-fourth, or one-half the embryo may when isolated produce all of the nuclei of a normal larva. The pressure experiments show, moreover, that even in cases in which isolated blastomeres will not produce whole larvæ, these same blastomeres, if all together, may be shuffled like a pocket full of marbles and yet produce perfect larvæ. Evidently we must seek some cause other than qualitative divisions to explain differentiation.

According to Weismann's theory of determinants, we must not only have qualitative divisions, but the cells of the body must become diverse by a process of self-differentiation. That is to say, the cause of differentiation lies within the cell itself and not only within the cell but in the idioplasm residing in the nucleus. There is no room left in this process for the effects of external conditions. Hertwig, on the other hand, maintains that external conditions form a very important factor in differentiation. That this must be true is demonstrated by the numerous modifications of form that occur as reactions to external stimuli. (See article *Differentiation*.)

It should be borne in mind in this connection that if the idioplasm resides in the nucleus, as we have reason to believe that it does, then the yolk and other constituents of the cytoplasm in the same cell form part of the external conditions relative to the idioplasm. Since the days of Balfour morphologists have universally accepted the belief that the presence of yolk has a profoundly modifying effect upon the course of cleavage.

Morgan and Driesch have presented experimental evidence that not only is this true, but that later stages may be affected by the presence or absence of portions of the yolk in the egg.

Weismann's theory of determinants breaks down, then, when examined critically in the light of the most recent observations. Let us see now what Hertwig would give us in place of it.

According to Hertwig, the fertilized egg is after all merely a cell, and can have no characteristics other than those that properly belong to cells. The impulse for the first division comes either from the nucleus or the centrosome, but the plane of the division is determined by the shape of the egg, the distribution of the deutoplasm, its

relative amount, the plane of union of the pronuclei, and so forth. For example, if the egg is oblong, the plane of cleavage will be at right angles to the long axis. If there is more deutoplasm, yolk granules, in one side of the egg than in the other, the egg will divide unequally, the larger segment including that part of the egg which is richer in deutoplasm. In the next stage internal structure of the blastomeres again may have a controlling effect. Blastomeres may again divide unequally for the same reason as before, and those which are the less cumbered with deutoplasm will divide the more rapidly. Now another factor comes in, for as soon as the organism consists of more than one cell, the interaction of one cell upon another affects the mode of cleavage and the differentiation of the cell. At the same time the cells are being affected by stimuli from without the organism, such as light, heat, gravity, and chemical composition of surrounding media. Although the cytoplasm may divide into parts differing in composition and specific gravity, the division of the idioplasm in the nucleus is always *quantitative* only. The two daughter nuclei are exactly alike. Nevertheless, the nucleus controls the differentiation of the cell, and this is affected by the different idioblasts which become active in different nuclei. Which idioblasts shall become active in any cell is determined by the different positions of the nuclei relative to the whole mass and the consequent difference in the stimuli that they receive. Hertwig quotes with approval the remark made by Driesch that "the differentiation of the cell is a function of its position."

There is no preformation of the embryo in the egg. The mosaic theory of the cleavage is a myth, and it is still more mythical to carry this mosaic idea back to the idioplasm of the egg. Preformation exists only in so far that the structure of the egg as a whole determines the character of the first cleavage. The structure of the whole embryo in the two-cell stage determines what the next step in development shall be. *The new characters that appear in ontogeny are really new formations* and not merely the becoming visible of pre-existing latent possibilities. The form of the embryo is the resultant of two factors, viz., the character of the idioplasm, and the nature of the stimuli to which it is subjected. Of these stimuli, those which arise within the organism are the most important in ontogeny, for they are the ones that are constantly changing as development proceeds. The character of the idioplasm determines primarily what the reaction shall be to any given stimulus, and this reaction in turn determines what the stimulus shall be in the next stage. Development is purely a process of epigenesis, and each stage determines only what the next stage shall be.

Wilson takes a position that is somewhat less advanced than that held by Hertwig. He points out that while it is generally true that the relative position of a blastomere determines what shall develop from it, this relation cannot be a purely geometrical or mechanical one, for in different species of eggs blastomeres may exactly correspond in origin and relative position, yet have entirely different morphological value. This is strikingly shown by a comparison of the polyclade egg with that of the annelid or gasteropod. Cells with exactly similar geometrical relations give rise to entirely different organs in the two groups.

Wilson agrees with Hertwig that the differentiation of the cytoplasm in one stage has a determining influence upon the next stage, and he explains the difference between eggs of the gasteropod and the medusa in the ability of single blastomeres to produce a whole embryo by supposing this differentiation to have begun in the former early in the history of the ovarian egg. He does not agree with Hertwig in supposing the somatic nuclei to retain their embryonic character. He points out that the facts of regeneration indicate that the nucleus has undergone a change, and he suggests that the change may be due to a process like that observed in the somatic cells of the segmenting egg of Ascaris. That is, the somatic nuclei do really differ from germ nuclei, but this is because they have given up part of their substance to the cytoplasm, and not, as Weismann would suppose, because they have undergone qualitative division.

Conclusions.—We have now completed a review of the principal fundamental conceptions to be found in theories of heredity. We have seen that the animistic theories belong to the age of mysticism, and receive no confirmation from scientific investigations. We have seen that there is reason to believe that heredity has its foundation in a physical basis, which is the protoplasm of the cell; and this may perhaps be differentiated into physiological units of some kind. Further there is much evidence from observation and experiment to show that the physical basis for heredity forms an idioplasm residing in the nucleus of the cell and more especially in those parts of the nucleus which are composed of chromatin. Whether the idioplasm of the germ cell is essentially different from that of somatic cells is doubtful. The view that such a differentiation does exist is strongly supported on morphological evidence in the single case of Ascaris. The physiological evidence is clearly against a qualitative division of the idioplasm. On the other hand, it indicates some sort of progressive differentiation in the idioplasm of somatic cells during development, a differentiation which begins earlier or later in different species. The causes of this differentiation appear to lie partly within the idioplasm itself and partly in the conditions surrounding it. Both experiment and common sense favor the view that the cell can contain no elements presenting other than purely cellular characteristics. Development is essentially a process of epigenesis. There are as many species of germ cells as there are species of organisms, and the germ cells of any single individual have probably the same degree of variability that other serially homologous organs of that individual have. The normal offspring is similar to its normal parent, because the germinal idioplasm of the two are of common origin, and both have developed under normal conditions. There is no evidence that the germ cells in an adult organism may be affected in any direct way by any changes that may take place in the cells of the body. Therefore the inheritance of acquired modifications of somatic cells is theoretically improbable.

Robert Payne Bigelow.

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HEREDITY IN RELATION TO THE DEVELOPMENT OF MORBID STATES.—It is almost of the nature of a truism to state that morbid conditions are and can only be either inherited or acquired; yet we are apt to confuse these two modes of production; hence in dealing with heredity as a factor in the development of states of disease it is essential at the outset to lay down clearly what is and what is not inherited. A little consideration shows us that only that is inherited which is the property of the individual at the beginning of the existence of that individual, for once existence has begun any disturbances set up by influences from without—by injury, infection, or intoxication—are obviously acquired. Now individual existence certainly does not begin at the moment of birth; it begins at the moment that the nuclear material of the spermatozoon fuses with the nuclear material of the ovum to form the fertilized cell. Hence that only is inherited which has been conveyed to the individual by the spermatozoon or the ovum, or which directly results from the fusion and interaction of the substances of these two parental cells.

It follows, therefore, that conditions acquired by the individual during intra-uterine existence must be carefully separated from inherited states.* Thus we have to divide morbid conditions into:

A. *Inherited.*
(1) From the father.
(2) From the mother.
(3) Resulting from the interaction of the paternal and maternal germ plasms.

B. *Acquired.*
(1) Of antenatal acquirement.
(2) Acquired during parturition.
(3) Of postnatal acquirement.

In our determination of what is truly inherited we have to recognize that infection as such cannot be inherited; syphilis and tuberculosis, for example, cannot be spoken of as inherited conditions. Not that these infections of the parent may not tell upon one or other of the conjugating germ cells and so lead to disturbed states of ovum or spermatozoon which may materially influence the resulting individual; such indirect influences may, as I shall point out later, lead to the manifestation of *parasyphilitic* and *paratuberculous* lesions; but the actual infection cannot be inherited. There is no such thing as inherited syphilis in the proper sense.

For such infection presupposes the passage of microbes from one or other parent to the offspring through the instrumentality of the germ cells. Apart from the fact that such microbes cannot strictly be regarded as properties of the parental organism, and apart from the fact that the spermatozoon, the germ cell through which this transmission is supposed often to occur, is so small and of such a structure that it cannot be conceived as a carrier of microbes save by adhesion to its exterior, were a microbe or microbes to gain entrance by any means into the ovum, that would be at the most a fortuitous inclusion, and we are not justified in imagining that it could be present without so seriously injuring the cell as to render it barren or monstrous. As a matter of fact the laborious observations of Gärtner upon the number of tubercle bacilli present in the semen of tuberculous guinea-pigs have demonstrated that the probability of a bacillus-bearing spermatozoon fertilizing an ovum is so extraordinarily minute that it may be neglected, while the statistics of Chiari upon the specific lesions of infants suffering from antenatal syphilis show that the liver is the organ most extensively involved in nearly all cases—a sure indication that the channel of infection has been from the placenta; for the blood coming from the placenta first passes through this organ, which thus bears the brunt of the infection.

The not infrequent cases in which a syphilized father begets syphilized children without the mother showing signs of general syphilis, must therefore be due to intra-uterine infection, either by passage of the specific virus from the uterine cavity through the cells of the amniotic sac (this has recently been shown possible in connection with other pathogenetic microbes), or by local infection of the fœtal placenta from the uterine cavity, or by *local* infection of the uterine mucosa and maternal placenta without extension of the disease in the mother, although with conferment of relative immunity upon the mother.

Having now cleared the ground it is possible to discuss the effects of heredity pure and simple. The inheritance of morbid conditions may be: 1. Specific or ex specie, *i.e.*, peculiar to all the members of a species. 2. Racial. 3. Familial. 4. Individual.

1. EX SPECIE.—This shows itself mainly in predispositions to certain infections including the disturbances set up by the grosser parasites. The infectious diseases of cold-blooded animals, for example, are quite different from those of warm-blooded, and, while some diseases occur inc ommon, the diseases to which man is liable are, as a series, well differentiated from those affecting cattle. Certain infections like syphilis, gonorrhœa, and typhoid would appear to affect man alone under natural conditions.

An interesting line of thought has been touched upon by Bland Sutton in his "Introduction to General Pathology," where he points out that certain structural features so characteristic as to be differential in certain species and races, are essentially inherited morbid conditions or malformations. He notes that the race of tailless trout of Islay (and we may add the race of Manx cats), the albinic or non-pigmented species of snails; the Chætodon with its remarkable osteomatoid enlargements of the bones, the race of horned men of Akim in Africa with their huge symmetrical exostoses of the malar bones, are all examples of such morbid inheritance. He is inclined to believe that horn and horny outgrowths in general have originated as pathological states, and what is more he would regard the descent of the testicle into the scrotum in man, and other animals which assume the more or less erect position, as an inherited anomaly. Another good example of inherited pathological structures is the pair of "castors" situated on the inner side of either foreleg of the horse. These familiar objects are of cuticular origin, are horny and unconnected with bone; they are constant and apparently useless. The only satisfactory explanation he can suggest for the inheritance of these anomalies is that some prepotent ancestor of the horse conveyed this to its descendants along with other more valuable properties; in other words, that there is a certain correlation in the inheritance of variations.

2. RACIAL.—Among the members of one species those of a different race show peculiar susceptibilities. Thus among the lower animals, the "Buffel" or native cattle of Austria-Hungary have been found largely insusceptible to tuberculosis, in this differing widely from ordinary domestic cattle; the race of Algerian sheep is refractory to anthrax when ordinary domestic European breeds are peculiarly susceptible. Numerous similar examples can be cited among the races of mankind; negroes are peculiarly liable to succumb to tuberculosis, they suffer from sleeping-sickness, ainhum, etc., and on the other hand appear not to be so susceptible to malaria as are white races. Malaysians show a marked tendency to contract beri-beri, they and the Hindoos (though to a somewhat less extent) and Eastern peoples in general are more liable to contract and to die from the plague than are those of European descent, although the latter show themselves more susceptible to yellow fever. In Canada, as in France, the greater severity of scarlet fever when it attacks those of Anglo-Saxon descent as compared with those of French origin is distinctly noticeable. I have already in the previous paragraph cited some examples of the racial inheritance of anomalies.

* Chantemesse and Podwyssotsky suggest for the former the term "Uterine Inheritance." I strongly object to this on the ground that in discussing inheritance, we who deal with one branch of biology must conform to the usage of those working in other branches. Intra-uterine existence is characteristic of only one division of animals and that a somewhat limited one. To speak of intra-uterine acquirement as inheritance is a sure means of continuing the present confusion which exists among medical men in connection with this subject.