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EMBRYOLOGY AND ITS RELATIONS[1]

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IT is my impression that what is expected of a retiring chairman is that he inform the section upon the "state of the nation" in his branch of science. Were I to attempt this in a phrase I should say that it was that of the Tower of Babel. On our program papers are listed by the hundred and are presented in various scientific languages, only one or two of which I can speak, and many speakers are talking at once, to the bewilderment of would-be listeners.

In contrast let us go back to the corresponding meeting forty years ago, when the American Society of Zoologists was called the American Morphological Society. Thirty-five papers were presented, four of them by title. A number of them dealt with the centrosome. There were several on biometry, but only one experimental study—that by Davenport on "The Rôle of Water in Growth." Dr. Minot described his newly invented rotary microtome. It is safe to say that had a Rip Van Winkle gone to sleep after that meeting and not awakened until now, he would have scarcely understood any of the papers on this year's program.

One wonders about the origin of all this present commotion, whether it does not go back to the instincts of primitive man—the nomadic hunter and the unskilled tiller of the soil. In his contact with nature he must have been impressed by the great diversity of living creatures as compared with the inorganic, and by their mysterious coming and going. Naturally he was most interested in those animals and plants that afforded food or were otherwise of practical im-

[1] Address of the retiring vice-president and chairman of the Section on Zoological Sciences, American Association for the Advancement of Science, Atlantic City, December 30, 1936.

portance, but many other creatures must have been recognized as indirectly related to his welfare and so have aroused his curiosity. Mystical notions regarding their nature were woven with practical knowledge into a sort of primitive fabric of science and religion not yet altogether disentangled.

Again in the modern development of biology whims and fancies have played a large part; else how can we account for the perverse interest in all the strange things included in the program of our meeting or typified in the appendages of the fabled paleozoic cockroach? A student once said to me that he could conceive of no greater pleasure than that of describing a new species of Staphylinid beetle. My own interest in the development of the fins of fishes was early raised to a pitch; but when I told a lady that I was writing my thesis on this subject, her reply was, "What earthly good are fins? I never eat them." To the layman such aberrations of taste are beyond comprehension. In fact, there is no easier way of holding up learning to public scorn and ridicule than to repeat the titles of Ph.D. theses.

The element of luck has also entered significantly into the development of biology, as in most other lines of human endeavor, not that it does not require intelligence to recognize luck when it comes and perseverance to gather its fruits. I recall a visit to Schermerhorn Hall, about 1910 or at least before the Drosophila visitation. Morgan waved with his hand at rows of bottles on shelves and said: "There's two years' work wasted. I've been breeding those flies for all that time and have got nothing out of it." Much progress has depended upon the fortunate findings of organisms that illustrate this or that principle clearly or such as submit to the most ruthless experimentation. Whole fields of knowledge have depended upon circumstances that are fortuitous as far as the subject itself is concerned. Take, for instance, biparental inheritance. Though it is said to have "Brought death into the World, and all our woe," think what would have been the present state of biology without it! Not to speak of the general drabness of life that would have prevailed, there would have been no genetics. We should have been robbed of the means of studying genes and might even not have suspected their existence. The chromosomes would have remained a perpetual enigma. Embryology would have had to go its way without the help of merogons and hybrids.

Some years ago I had the honor to address you as retiring president of the American Society of Zoologists. My subject was "The Return to Embryology," and my remarks included a certain amount of prophecy which has since come true. I trust, therefore, that you will grant me the indulgence of recalling some of the things then said, especially since they have not found their way into print.

Referring to the fact that all sciences have their ups and downs, it was pointed out that embryology was then (1925) in a period of depression, from which there were signs of emergence. The "organizer" had just been named. Its effects had been discovered some years before, but the importance of Spemann's work was not then so generally recognized. There were a few centers where work in experimental embryology was going on, but the flare-up and the great expectations of the 1890's and the first decade of the present century had subsided. The difficulties of understanding the development of organisms seemed to many insuperable, and no wonder.

> The living embryo changes continually; its form, its mechanisms and its functions change; its parts function while changing. These transformations are themselves functions. We have, then, superposed on the ordinary functions of nutrition, respiration, protoplasmic and nervous transmission, action of internal secretions circulating in the internal medium, etc., a whole system of developmental functions, which, as far as we have been able to find out, are totally different from the former. The embryologist has, therefore, a problem of a higher order of complexity—a superproblem—to contend with than has he who directs his attention to the study of the structure or function of the finished organism.
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> This is usually overlooked. Embryology, from its close relation to comparative anatomy and from the employment of schemata to represent its processes, came to bear the reproach of physiologists that it was a morphological science and on that account dealt with statics and not kinetics. A moment's consideration shows this view to be altogether erroneous. The organism never reaches a state of rest until it has run its course or is securely preserved in a bottle. The physiologist accepts the finished organism as given and endeavors to find out how it works. The embryologist, on the other hand, attempts to show the origin of the mechanisms which the physiologist is content to accept ready made for study. May not the embryologist, then, return the reproach and say that the physiologist is merely looking for something easy to do?[2]

After the first harvests from the virgin field of experimental embryology had been gathered, the workers became impatient and soon landed on the barren ground of theory without the necessary factual equipment for further progress. "There was a time of discouragement. . . . The fertility of the soil seemed to have suddenly run out and tillage no longer worth while. What, more human, then, than the gold rush to genetics and general physiology?"[3] Later came another gold rush to endocrinology, now perhaps at its height.

For the embryologist those days of depression were

[2] Quoted from the 1925 manuscript.
[3] *Ibid.*

peaceful and inviting to meditation. Now in 1936 the predicted gold rush to our own territory is upon us and times are strenuous again. Our program shows two full sessions devoted to embryology, with many demonstrations, a symposium on genetics and development and many papers in other sections having a bearing on embryology. In one sense this is all satisfactory. The liaison between genetics and embryology is now established, but can we say the same of embryology and physiology? Perhaps we are still under the spell of the doctrine that more than one liaison at a time is sin.

There is a growing literature in physiological embryology, but it is still largely physiology of the embryo, as understood by the physiologist. Chemical embryology is also mainly of this kind. Our knowledge of the physical and chemical changes underlying development and differentiation is still deplorably meager.

We may distinguish in the organic world three degrees of transformation, taking place with velocities of three different orders of magnitude, and no doubt related, though precise knowledge of their relations is lacking.

(1) Those concerned with the maintenance functions of the organism—classical physiology.

(2) Those involved in the development or life history of the organism, which are in general of much lower velocity but are closely interwoven with the first group. They appear to be largely but not entirely irreversible.

(3) Those concerned with evolution or transformation of species.

Like the rate of change in the three successive categories of transformation, our knowledge of the processes involved is on a rapidly descending scale. Yet the field covered by the last has dominated biological thought for three quarters of a century! Fifty years ago Carl v. Nägeli, in his oft-cited but seldom read "Abstammungslehre,"[4] excoriated the physiologists for leaving their most difficult and crowning problem to others less competent to solve it, for, as he says, the theory of the origin of organic nature is of purely physiological character. While this phraseology would hardly be considered appropriate to-day in view of our extensive experimental morphology, Nägeli undoubtedly wished to emphasize the essentially functional nature of organic transformations, and the importance of an approach to the problem by experimental methods, which in his time, among biologists, were the possession almost exclusively of physiologists. That zoologists, botanists, anthropologists and paleontologists should have busied themselves with this great problem seemed only natural and highly desirable to Nägeli, but in their speculations they went, in his opinion, far beyond their limitations.

> The theory of evolution touches also philosophy and theology in very sensitive spots and interests the intelligent general public partly for this reason and partly because human vanity has always attached much importance to origin and relationship.
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> On this account we have seen philosophers, theologians and, in addition, literati of all sorts and conditions take possession of the problem. This too would have been quite in order, if every one had but utilized the established results of scientific investigation for his own field and had rendered to his own circle a clarifying and instructive account of them; and if so many had not considered this field of difficult physiological problems to be a free-for-all arena for senseless argumentation.[5]

Because of early theological opposition, the theory of evolution became for its advocates a sort of religion itself, and not so long ago in this country we witnessed a veritable fundamentalist battle with theological fundamentalism on the one side and evolutionist fundamentalism on the other. The scientific investigation of evolution has suffered severely from this emotional conflict.

While it can scarcely escape any one accustomed to scientific thinking that the processes of evolution can be elucidated only by painstaking experimental work carried on over a long period of years, the short cut to knowledge by the speculative route still holds out great allurement to those whom Huxley called paper philosophers. Even with carefully controlled continuous experimentation, the enormous time involved in evolutionary changes, as compared with the life span of the individual investigator, and the difficulty of devising standards of reference that will hold constant throughout long intervals of time will render the measurement of such change very uncertain. Nevertheless, the development of modern genetics, the experimental study of the origin of mutations and the new mathematical theory of natural selection are hopeful signs of the applicability of exact methods to the study of evolutionary processes.

The difficulties of investigating embryonic development are of a different nature. The velocity of the changes is rapid enough and they may be observed repeatedly, so that experiments are readily carried out, but the scale is minute and a great variety of transformations which are inextricably interwoven are going on at the same time. It is not strange, therefore, that the experimental embryologist has gone ahead wherever a promising lead seemed to open,

[4] C. v. Nägeli, "Mechanisch-physiologische Theorie der Abstammungslehre." München u. Leipzig. R. Oldenbourg, 1884.

[5] *Op. cit.*, p. 4.

without much thought of building up a comprehensive and internally consistent system.

The reference of developmental processes to the cell was the most important step ever taken in embryology. The mutual relationship of the two primary constituents of the cell, nucleus and cytoplasm, both of which are concerned in the development of the organism, has naturally come in for much study. A number of fruitful lines of investigation bearing on this question have been followed, from which it is now generally recognized that, with few possible exceptions, the nucleus in the end controls the character of the combination. It is not to be lost sight of, however, that the nucleus can only work in cooperation with cytoplasm that is not too far removed from it systematically.

From the fact that genes, which are assigned to the nucleus, are studied mostly in relation to small mutations, it has been suggested from time to time that they are concerned only with the development of such minor characters and that the more fundamental qualities of the organism are fixed in the cytoplasm. This can hardly appeal to one who thinks the question through. The impression rests rather on the present limitations of our methods of study than on the limitation of gene action itself. We can not test by current experimental methods the effect of genes on cytoplasm of too remote origin.

The location of genes in the chromosomes, the proof of their linear order, the association of somatic characters with definite points in the chromosomes, in short, the whole development of the gene theory is one of the most spectacular and amazing achievements of biology in our times. The embryologist, however, is concerned more with the larger changes in the whole organism and its primitive systems of organs than with the lesser qualities known to be associated with genic action. As Just remarked in the symposium this morning, he is interested more in the back than in the bristles on the back and more in eyes than in eye color.

Now that the necessity of relating the data of genetics to embryology is generally recognized and the "Wanderlust" of geneticists is beginning to urge them in our direction, it may not be inappropriate to point out a danger in this threatened invasion.

The prestige of success enjoyed by the gene theory might easily become a hindrance to the understanding of development by directing our attention solely to the genom, whereas cell movements, differentiation and in fact all developmental processes are actually effected by the cytoplasm. Already we have theories that refer the processes of development to genic action and regard the whole performance as no more than the realization of the potencies of the genes. Such theories are altogether too one-sided.

Whether we accept the plasmon concept or not, we are obliged, for reasons above stated and others as well, to assign to the cytoplasm of every egg specific characters, which are different in each species of organism. In the egg there are characteristic local differentiations, which are frequently of the nature of inclusions, but after these are all accounted for, the specific character of the cytoplasm still persists in the ground substance.

Living protoplasm is a complex mixture of substances deriving its properties not merely from their chemical nature but also from their arrangement in space. Nearly all are agreed that it is to the protein constituents of protoplasm that we must look for specific characters, though there are also specific carbohydrates and lipoids.

Much has been learned about the chemistry of proteins since the turn of the century, and about their physical properties and structure. Accordingly, on a recent occasion[6] I made the attempt, taking heart from Needham and others, to refer the changes in the developing organism to the conditions imposed by the configuration of the protein molecule and its accompanying chemical and physical activities. Lest you take me to task for resorting to such crude conceptions, look at the biochemists and their zoomorphisms, their protein molecules with backbone, head, tail, limbs and even back and belly, as well as right and left sides.

It was suggested that the dipole character of these molecules would tend to orient them within the cell, possibly with respect to the point of attachment in the ovary, thus bringing to expression the primary polarity of the egg. Opposite chemical properties at the two ends would set up different reactions resulting in the formation of different substances which are carried to opposite poles by electrophoresis. Two complementary fields or material gradients would thus be formed, each extending from a region of maximum concentration at one pole to a region of minimum concentration at the other. These materials, as well as substances of genic origin entering the cytoplasm from the nucleus, would start up new reactions of varying regional intensity in the side chains of the protein molecules, according to the concentration of the primary gradients. Thus new centers and fields of chemical activity would be set up locally, and in each such region new reactions would take place with other side chains, the relative velocities of these reactions being of significance.[7] The result would be a

[6] Harvard Tercentenary Conference.

[7] R. Goldschmidt, "Physiol. Theorie d. Vererbung." Berlin, Springer, 1927.

greater and greater local diversity of action, with accompanying local differentiation of cells, as the original egg became more and more divided. This latter process has often been referred to as segregation, but it is more correct to call it localization, for it seems to be an essential of the developing organism that, while new differentiating substances are formed, all cells retain not only in their nuclei but also in their cytoplasm the same fundamental specific characters as are possessed by the egg cell. In other words, some of the specific protein molecules, with their potentialities for characteristic arrangement, remain unchanged throughout the organism.

The chemical changes may be assumed to be accompanied by changes in molecular configuration involving the constants of atomic spacing. Hence through the action of crystallization forces, new internal stresses and strains arise, which are relieved by change in shape of the cells. The movements of gastrulation, the formation of the medullary plate and its rolling up to form a tube may be ascribed to the action of such forces.

Differentiations are in a sense, then, the by-products of protoplasmic activity and are accompanied by movements involving change of form. After the chemical changes have gone to a certain point, they tend more and more to inhibit other local reactions, and finally the cell becomes so loaded with secondary material that reverse changes no longer occur. It is customary to speak of regions, cells or cell groups, in which changes have proceeded so far, as "determined." In my opinion this expression were best dropped from the language of embryology, for there is no criterion for finding out when this condition is reached, if indeed it ever is. It is never possible to know whether some new set of conditions to which a developing part may be subjected may not undo what seems to have been already done irrevocably.

The striking experiment described by Schotté at the present meeting is a case in point. Here the regenerating blastema of the limb or tail of an amphibian, when placed in the eye of a frog larva from which the lens has been removed, differentiates into a lens. Already "determined" to form cartilage, bone and muscle in a certain definite configuration, this tissue, nevertheless, under the new and radically different conditions obtaining in the eye chamber, forms a crystalline lens, a structure heretofore known to develop either directly or indirectly only out of ectodermal epithelium.

Substances that react with the living protoplasm in the above way may arise from many sources. They may diffuse into the oocyte from maternal tissues; they may arise from the genes in the nucleus; they may come from organizers, *i.e.,* from other cells in close contact with the cells affected; they may be transported in later stages through the circulating body fluids (hormones), and finally they may come from the external medium. There is no reason to think that there is any fundamental difference in the action, on the living protoplasm, of substances derived from these various sources. Much depends, however, upon the time at which the protoplasm is most sensitive to their action.[8]

The importance of substances of genic origin lies in their continuous source of supply and in their transmissibility through generations. Organizers have come into prominence through the dramatic manner in which they have demonstrated epigenetic development at a time when the tendencies of thought were in the direction of preformation. Their most striking action, still veiled in mystery, lies not in the induction of a particular organ here or there, but in making plastic material form a harmoniously constructed embryo.

The discovery that various things could be substituted experimentally for the organizer has led to the effort to isolate a pure substance that will have the same effect. Likewise the discovery, in the body fluids of insect larvae, of factors mediating the action of genes has led to the search after their chemical nature.[9] This has been stimulated further by the circumstance that certain hormones known to have definite effects on the developing organism, such as thyroxin and the sex hormones, have been isolated in pure form and are of known structural formula. The very delicate and constant effects of these substances on development have been revealed in studies from many different quarters. All this is to the good, since if one substance taking part in a reaction is known, the chances of finding out what the other substances are and what the nature of the reaction itself is are much improved. However, it must not be lost sight of that we still know practically nothing of the actual changes involved in differentiation. Genetics by itself will not solve this problem. To accomplish this will require all the ingenuity of the embryologist, using the most refined methods of physics, chemistry and general physiology, not only those of the present but many others still to be invented.

Such features as pigmentation and pigment pattern in particular demonstrate the interaction of genes and hormones. The work from the Whitman Laboratory at the University of Chicago by Lillie and collaborators shows how rates of growth, genic action, rhythms of production of hormones, threshold values, all con-

[8] F. E. Lehman has discussed this question recently in a thoughtful address. *Die Naturwissenschaften,* 24: 401–407, 1936.

[9] A. Kühn, *Wissenschaftliche Woche z. Frankfurt a. M.,* Sept. 2–9, pp. 37–48, 1934.

tribute to the establishment of plumage patterns in birds. This deserves a high place among the achievements of experimental morphogenesis. Similar work on wing patterns in the Lepidoptera by Kühn and his associates in Göttingen has yielded comparable results. Such studies lend themselves admirably to the elucidation of quantitative relationships.

The form of gourds and of many other organic structures may be referred to relative growth rates, as Sinnott has clearly shown, and those features are likewise amenable to quantitative study. Here the unit character is not a particular form itself but a relative growth rate resultant in this form. At least four different types of form determination have been recognized in this group and are independent of each other in inheritance. "The genes which control them evidently differ in the time at which the major effect is produced and in the character of the effect itself."[10]

Growth is peculiarly susceptible to conditions imposed from without, particularly food, but growth rates are dependent also upon hereditary constitution. By means of heteroplastic grafting between species having very different growth rates, it is possible to show how the growth rate of any particular organ or part may be modified by associated structures and in this way to study quantitatively the interplay between hereditary and environmental factors of development.

A new method of study of protoplasmic structure is that of x-ray diffraction, and its possible applicability to embryonic differentiation is now in the offing. This whole field is but another romantic adventure of modern physics, though not so well known as some of the others of a more speculative nature. It is only twenty-five years since v. Laue's discovery that crystals could be used as diffraction gratings for x-rays. Applied at first to the study of crystals of some of the simpler inorganic salts belonging to the regular system, the method was soon extended to more complex salts and organic compounds. Cellulose, chitin and some of the simpler or denatured proteins have also yielded to this method of attack on the problem of their atomic arrangement. Even a few of the living tissues, particularly those occurring in fibrous form, such as tendon, muscle and nerve, have given clear diffraction pictures, now that very powerful x-ray tubes with appropriate accessories, necessitating only short exposures, are available. At the meeting of the British Association last September, according to a brief report in *Nature,* Dr. Mathieu gave a paper on what might be termed x-ray cinematography, in which the change in atomic spacing occurring in the nitration of cellulose was demonstrated.[11] Surely it is not too much to hope that some of the changes taking place in embryonic differentiation may some day be similarly revealed.

I have come to the close of a rather rambling discourse and can scarcely claim proof for many of the assertions made. If they seem to be vaguely general and to lack clarity, consider the following words of Max Planck:

> We must never forget that ideas devoid of a clear meaning frequently gave the strongest impulse to the further development of science. The idea of an elixir of life or of the transmutation of base metals gave rise to the science of chemistry; that of perpetual motion to an intelligent comprehension of energy; the idea of the absolute velocity of the earth gave rise to the theory of relativity, and the idea that the electronic movement resembled that of the planets was the origin of atomic physics. These are indisputable facts, and they give rise to thought, for they show clearly that in science as elsewhere fortune favors the brave.[12]

OBITUARY

ELIHU THOMSON[1]

No obituary notice can adequately express the significance of the life and accomplishments of such a man as Elihu Thomson, nor indeed is this a serious lack, for his name and fame are already deeply rooted in our American traditions of success and of technological progress. For purposes of record, however, and as a tribute to our colleague, who was so affectionately called "The Professor" by all his friends, there is presented the following biographical notice.

Elihu Thomson was born in Manchester, England, on March 29, 1853, son of Daniel and Mary Rhodes Thomson. The family moved to America when he was five years old, settling in Philadelphia. Progressing rapidly in elementary schooling, he was ready to enter the Central High School at the age of eleven. The rules of this school, however, required him to wait until he was thirteen to enter, and he employed the intervening two years in reading and experimenting in the new and fascinating field of electricity.

Once admitted to the high school, his academic progress was rapid. Graduating at eighteen, he was immediately made an instructor in physics, then an assistant professor at twenty and a full professor at

[10] E. W. Sinnott, *The American Naturalist,* 70: 245–254, 1936.

[11] W. T. A., *Nature,* 138: 824–825, 1936.

[12] M. Planck, "The Philosophy of Physics," p. 112. Translated by W. H. Johnston. New York, Norton and Co., 1936.

[1] Incorporating parts of an article in *The Technology Review,* Vol. 33, January, 1931.