Growth and Morphogenesis

Edmund W. Sinnott, *Yale University*

AN INDICATION of the great and continuing interest in the problems of organic development is the appearance of two volumes[1] of papers in this field. Those in the first volume were presented at a symposium of the Society for Experimental Biology held at Cambridge, England in July, 1947, and are now published under the title *Growth in relation to differentiation and morphogenesis.* Those in the second are an outgrowth of a conference on "The Chemistry and Physiology of Growth" held at Princeton in September, 1946, as part of the celebration of the Bicentennial of Princeton University.

These essays cover many of the fields of research in plant and animal development. They illustrate how the various disciplines of the life sciences are coming to focus on the central problem of the methods by which living matter produces those specifically formed and functioning structures which are so well termed organisms. Embryology, moving from its descriptive and phylogenetic beginnings to experimental attack, long ago began to study this question. Morphology, realizing that organic form is the visible expression of organization, began to seek the causes of form. Genetics, having outgrown its "classical" phase, is now engaged in the far more difficult problems of the mechanism of gene action and the relations between genes and the individuals which develop under their control. Physiology itself is concerned more and more with developmental problems. Various aspects of these fields are treated in the present volumes.

In the Cambridge symposium, the first paper, "The Role of the Cell in Determination" as illustrated by the metamorphosis of a blood-sucking bug, *Rhodnius,* is discussed by V. B. Wigglesworth, who suggests that "the supracellular fabric is a chemical continuum, a 'molecule' in the sense that it is held together by chemical bonds; and that it is the continuity of this substance from cell to cell which provides for the unity of the organism." It should be noted in passing that G. A. Baitsell presented this viewpoint in 1938 (*Amer. Nat.* 1940, **74**, 5–24).

[1] *Growth in relation to differentiation and morphogenesis.* (Symposia of the Society for Experimental Biology, No. II.) New York: Academic Press, 1948. Pp. vi + 365. (Illustrated.) $7.50.
The chemistry and physiology of growth. Arthur K. Parpart. (Ed.) Princeton, N. J.: Princeton Univ. Press, 1949. Pp. vii + 293. (Illustrated.) $4.50.

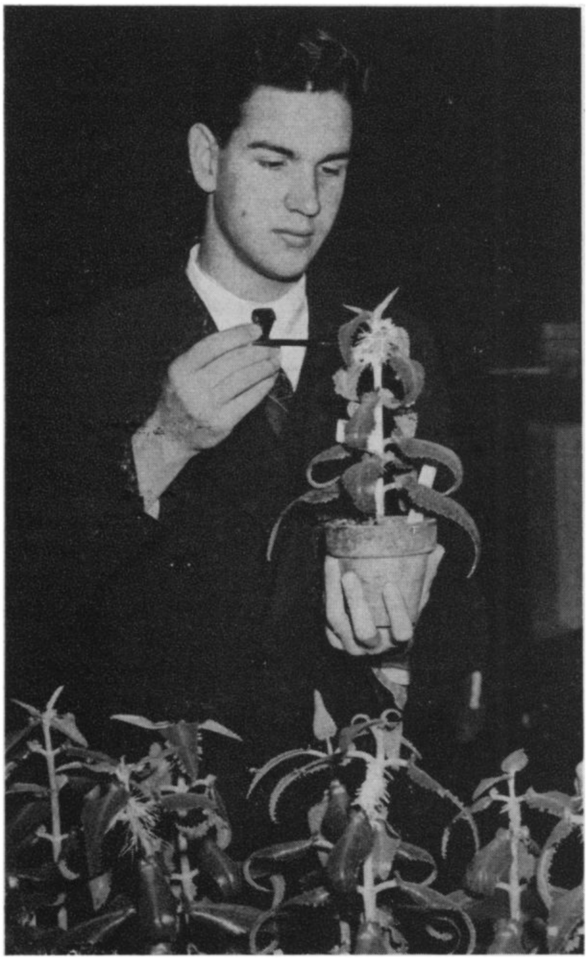
The next three papers are in the familiar tradition of experimental embryology and morphology. "Concepts on the Mechanism of Embryonic Induction and their Relation to Parthenogenesis and Malignancy," by J. Holtfreter, treats of embryonic induction in amphibia. The author believes that "the external stimuli capable of inducing these phenomena are unspecific and are related to each other merely by the faculty of causing the liberation and mutation of certain morphogenetic compounds (plasmagenes) which are self-reproductive." "On the Developmental Physiology of the Sea Urchin," by S. Hörstadius and T. Gustafson, discusses certain aspects of embryonic metabolism. In "Growth and Differentiation of Nerve Fibres" J. Z. Young describes the various processes concerned in the regeneration of nerves. Although we are beginning to gain some exact information about this process, the author thinks it unlikely that our knowledge of it will be quickly reduced to simple general terms.

These are followed by three papers in a related group dealing with factors concerned in the induction of flowering in the higher plants, especially photoperiodism, vernalization, temperature, and hormones. F. G. Gregory discusses "The Control of Flowering in Plants," presenting an excellent review of the various hypotheses which have been put forward; K. C. Hamner, "Factors Governing the Induction and Development of Reproductive Structures in Plants," with especial reference to "phasic development"; and R. Harder, "Vegetative and Reproductive Development of *Kalanchoë Blossfeldiana* as Influenced by Photoperiodism." With these should also be mentioned a paper which comes somewhat later in the volume, "Morphogenic Factors as Exemplified by the Onion Plant," by O. V. S. Heath and M. Holdsworth, which postulates two hormone systems controlling the formation of bulbs and of flowers.

P. J. Gaillard describes the culture *in vitro* of endocrine glands of man, especially the parathyroid, and their transplantation into patients suffering from glandular deficiency, with resulting success in effecting cures.

Five papers are concerned with one phase or another of the problem of gene action. C. H. Waddington in "The Genetic Control of Development" discusses various ways in which specific cytoplasmic proteins, essential for the origin of differentiation, may be produced. In "Nucleus and Cytoplasm in Differentiation" K. Mather treats of the same problem from a somewhat different viewpoint. S. Spiegelman, in "Differentiation as the Controlled Production of Unique Enzymatic Patterns," supports the plasmagene theory on evidence derived from a study of enzymatic adaptation and enzyme patterns in general. Hans Grüneberg in "Genes and Pathological Development in Mammals" considers a wide range of gene effects which result in pathological or atypical characters. Ernst Hadorn describes "Gene Action in Growth and Differentiation of Lethal Mutants of Drosophila."

In quite a different vein are four papers which are concerned primarily with the development and the arrangement of leaves on the plant axis. F. J. Richards in "The Geometry of Phyllotaxis and its Origin," reviews the complex phenomena of phyllotaxis and considers various explanations which have been proposed for it. Mary Snow and R. Snow, writing "On the Determination of Leaves," consider the same problem on the basis of their experimental studies. Evidence from extensive experiments on the shoot tip is presented by Ernest Ball in "Differentiation in the Primary Shoots of *Lupinus albus* L. and *Tropaeolum majus* L.," especially with reference to histological differentiation. C. W. Wardlaw in "Experimental Morphology with Special Reference to Pteriodophytes" shows that in these plants, where the terminal meristem is dominated by an apical cell, the resulting growth pattern is essentially like that of the seed plants, where the meristem is very differently organized.



Plants with roots growing from their tips as an illustration of the use of plant hormones in modifying growth and development. Early work was done by P. W. Zimmerman and A. E. Hitchcock of the Boyce Thompson Institute for Plant Research, Inc., Yonkers, New York. (*Science Service Photo.*)

The final essay, "Observations on the Present State of Embryology," by J. H. Woodger, is a plea for more attention to the construction of hypotheses in embryology, using the logical techniques now available. These hypotheses, which he thinks will probably seem very unorthodox, should be based not only upon biochemistry and X-ray crystallography, but upon the data of embryology itself, with the emphasis upon relational properties.

The Princeton volume contains ten essays, of which the first six are primarily concerned with growth rather than development. J. H. Northrop presents a general discussion of "Enzymes and the Synthesis of Proteins," with an extensive bibliography. F. O. Schmitt, in "Molecular Morphology and Growth," describes our knowledge of the fibrous proteins, and offers some suggestions for fruitful fields of study in connection with protein molecules generally. K. V. Thimann, in "Plant Growth Hormones," reviews the multiple effects of auxin on growth, especially with isolated plant parts. K. Folkers, in "Unidentified Vitamins and Growth Factors," describes a considerable series of these and their properties. C. B. van Niel, in "The Kinetics of Growth of Microorganisms," points out that with modern techniques for turbidity measurement growth studies on populations of such organisms can be readily made, and the kinetic aspects of growth analyzed. E. S. G. Barron, in "Cellular Metabolism and Growth." shows the relation between metabolic processes and the growth and division of cells.

The last four pages are of more particular interest to students of development and morphogenesis. Paul Weiss here treats at some length the problem of "Differential Growth." He discusses cellular differentiation primarily in molecular terms, emphasizing molecular "ecology" and the importance of organization at cell surfaces. Growth, and especially its orientation and the elaboration of growth patterns, must be referred, he believes, to cellular differentiation, although behind it all, and not reducible to molecular terms, there is still a prior topographical organization to be reckoned with. There is no single master clue, he believes, to differential growth or to growth in general.

J. S. Nicholas discusses various "Problems of Organization," including nucleo-cytoplasmic relations, egg constituents, organizational dependencies, independent movements, mass movements, chemical organization, and regeneration, as illustrated in the embryology of amphibia, Drosophila, and the chick.

C. P. Rhoads approaches the problem of development through a study of "Neoplastic Abnormal Growth." He stresses especially the importance of genetic changes in the production of cancer, although self-perpetuating cytoplasmic factors and virus bodies cannot be neglected. "The neoplastic process," he believes, "is a distinctive, characteristic sort of abnormal growth, malignant as well as autonomous, something more than a quantitative deviation from the normal rate and extent of differentiation."

In "The Adrenal Gland, a Regulatory Factor," C. N. H. Long discusses the regulatory interplay of three elements of the endocrine system—anterior pituitary, adrenal cortex and medulla—and pays particular attention to the role of adrenal cortical hormones in hastening the translocation of intact cellular protein molecules to all parts of the body.

The variety of topics discussed in these volumes testifies to the wide diversity of viewpoints from which the problems of morphogenesis are being attacked and raises the question as to whether this field of biology does indeed have a content of subject matter and a program of specific objectives sufficiently different from other fields so that one is justified in treating it as a distinct discipline. Is it simply one kind of morphology, or physiology, or genetics, or is it different enough from all the rest to stand on its own feet?

The answer to our question, I think, is given in the very name morphogenesis itself—*the origin of form.* Perhaps the most distinctive aspect of living things is that they possess specific forms, those constant patterns of external and internal structure by which they can be recognized. What makes this fact significant is that form is the outward and visible expression of biological organization. Needham has well said that "the problem of organization is the central problem of biology, and the riddle of form is the fundamental riddle." Morphology deals with form, but in a descriptive and comparative manner only. So do its related disciplines of histology and anatomy. Embryology is concerned with the development of form but not its cause. Unlike these, morphogenesis endeavors to understand the mechanisms involved in form development and the fundamental causes which are responsible for it, thus striking at the heart of the problem of organization itself. Other biological sciences deal with other aspects of organisms—with their metabolism, their heredity, their evolution, their environmental relations or their classification—but only morphogenesis is concerned specifically with the problem of their organization, of what really makes them *organisms.* Morphogenesis as distinguished by its objectives thus occupies a unique position, and in a sense the topmost one, in the hierarchy of biology and seems clearly to deserve recognition as a distinct discipline.

If this is true, why should morphogenesis in practice often seem so diffuse, so fumbling? The answer is not difficult. It has, to be sure, a definite and unique goal, but this goal is one of extraordinary difficulty, since in a real sense it is the problem of life itself. It involves not only techniques of analysis, in which science is so completely at home, but the much more difficult ones of synthesis. It is concerned not only with specific substances, but more particularly with specific *relations.* The problem of organization, as the history of biology shows, is extraordinarily resistant to central attack. We can make forays into one corner of it or another, but to strike successfully at the citadel itself is so difficult that it may require tools and techniques which as yet we do not possess. It is no wonder that the morphogeneticist, circling around the periphery of his great objective, is often at a loss how to make a direct approach to it, and that his efforts frequently seem halting and ineffectual. What distinguishes a biologist when he is working in this field is not his methods, but the character of his objective.

What can the morphogeneticist do toward the solution of his problem? The volumes here under review show some of the lines of attack open to him. Much of a purely descriptive character, like Dr. Richards' analysis of phyllotaxy, yet remains to be done. In the minds of many, unfortunately, such work often suffers from the fact that it does not deal directly with causes, that it is not primarily experimental, that its conclusions do not seem to strike at the root of the matter. And yet such work is absolutely necessary to an understanding of the problems that are to be attacked, and often provides important clues for further progress. Certainly the concept of allometry, which has made it possible to express by single constants the relative growth of parts or dimensions, has simplified many of the complex phenomena of development and has made it possible to present to the physiologist a much more concrete problem than would have been possible before the use of this new technique. D'Arcy Thompson's demonstration that one organic form may be transformed into another by the regular deformation of a coordinate system in which it has been inscribed, and that any modification of this form affects the whole system rather than a local part of it, is surely not without significance for an understanding of the integrating factors in development. The student of morphogenesis in his haste to use the methods of his colleagues in physiology and biochemistry should not neglect this descriptive part of his problem, for it may well point the direction in which he must guide his steps.

Of course the morphogeneticist also employs the techniques and draws upon the data of other fields of biology, as well as of biochemistry and biophysics, and most of the progress which he has made has come in this way. An analysis of the amphibian organizer is clearly one important line of attack. So is the study of how photoperiodism, temperature, mechanical factors, and phytohormones affect the development of plant structures. No analysis of development can be complete unless it considers the role of enzymes, nucleoproteins, and other factors which are primarily biochemical in their nature. Molecular morphology and ecology must be considered. The fine structure of protoplasm cannot be neglected, nor the evidence now available from electron microscopy. Certainly without an understanding of gene action no sound theory of morphogenesis can be built. These methods of attack and many others are open to the morphogenetic practitioner and it is here that most of his efforts at present are being exerted. Their wide diversity is what sometimes lays him open to criticism as a man who cannot make up his mind as to where he is going. He knows where he would like to go, but it is extraordinarily difficult to discover the way thither.

Temptations often beset anyone who undertakes to work in morphogenesis, temptations to oversimplify his problems, to regard as a solution something that is only a first step toward it. He is inclined, for example, to look for "formative substances" which by themselves control the development of specific structures. Many specific substances are certainly important in developmental processes and their study has done much to increase our knowledge of the mechanism of growth control. But it is naive, I think, to believe that any substance, however potent, can *of itself* determine a particular organic form. We should remember the words of J. S. Haldane, that "we are faced with the question how this particular substance is present at the right time and place, and reacts to the right amount to fulfil its normal functions." The substance is merely the agent of something more fundamental, of that "prior topographic organization" of which Dr. Weiss speaks. In the same vein, Dr. Woodger in his essay calls attention to the fact that many biochemical reactions take place quite differently inside a living organism from what they do *in vitro*. We should recognize that such substances do their work not directly, but by their effects on a system of organized relations through which the ultimate control is exercised. To stop anywhere short of an understanding of such a system is to fail in the ultimate aim of morphogenesis, however valuable and necessary any preliminary steps may be.

Of course to gain such understanding is remarkably difficult. Relations seem to be much harder things to study than atoms, but we should not hesitate to explore the problem as well as we can. The idea that Dr. Wigglesworth proposes, for example, that the whole organism is a chemical continuum and thus comparable, perhaps, to a single molecule, is such an exploratory attempt, and poses a problem which can be attacked. The possible relation between the form of protein molecules and that of the organism in which they occur may well be a fruitful idea. The whole concept of morphogenetic "fields," vague as it is, is a step in the same direction. The problem we are here facing is one of the ultimates. It may well require for its solution something more than the well-established concepts with which biology has chiefly dealt. Here is the place for those new, adventurous, and unorthodox hypotheses for which Dr. Woodger pleads, hypotheses which are not vague and hazy but which can be tested by techniques now available to biologists.

The present volumes are a challenge to all students of development, for they not only present the results of some very significant work in this field, but raise again the question of what morphogenesis is and ought to be, and point to the great enigma with which every student of biology is ultimately faced and which it is useless to evade or minimize—the problem of biological organization, which is really the problem of life itself.