NEW PATTERNS IN GENETICS AND DEVELOPMENT

C. H. WADDINGTON

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Preface

THIS book is based on a set of six Jesup Lectures, given at Columbia University during April and May, 1961. An invitation to contribute to a series as well known as this faces its recipient with a somewhat daunting challenge. He is, I suppose, expected to produce something new; something, moreover, which falls a bit outside the regular well-charted paths of scientific advance of which everyone is already fully aware; and finally, something of his own. My attempt to meet this challenge takes the form of a discussion of two problems, one rather new and one very old. The new problem is the impact of the recent great advances in genetics on our understanding of the development of multicellular organisms. This subject has often been touched on by geneticists but has received less attention from authors who are fully conversant with the embryological material. The old problem is the ancient conundrum of morphogenesis—the appearance of organized structure within a vast range of sizes from the cellular organelle to the elephant. Present-day biology, which is dominated by the enormous successes of biochemistry, has tended to neglect these structures which are too large to be handled by biochemical methods; but they still confront us as one of the most insistent and least understood characteristics of living things. Some may feel that the sensible thing to do at present about these structures is to leave them alone in hope that the progress of biochemistry will eventually throw up some new clue; but to others, including myself, they have the attraction of a real frontier, a region where one is not just trying to fill in an already existing sketch map, but where one has to try to figure out the bare bones of the geography from scratch.

A short set of lectures such as this cannot, of course, attempt to be comprehensive in the treatment even of the topics chosen for discussion, and the desirability of describing some of the work of my own laboratory

has led to what would have been an even greater imbalance if I had set out to give a general survey of modern embryology. I have, for instance, consciously left out many important topics on which the main recent contributions have been made by American biologists, since these are matters which scarcely need exposition by a visitor.

There is today in America a great flowering of developmental cell biology as well as of genetics. To an outsider it is perhaps surprising that there is not more contact between the two fields in this country; but I should not like my friends in either camp to feel that the omission from this short series of lectures of many of the topics nearest their hearts is due to any lack of appreciation on my part of the magnificent advances which are being made.

New York, Middletown,
and Edinburgh
March–August, 1961

C. H. WADDINGTON

Acknowledgments

DURING the preparation of these lectures, I had the good fortune to be invited to become a Fellow of the Institue for Advanced Studies at Wesleyan University, Middletown, Connecticut. There I was provided with ideal conditions for thinking and writing, without which it would have been difficult indeed to step back from day-to-day preoccupations and take a look at the problem of development as a whole, as I have tried to do. To the Director of that Center, Dr. Sigmund Neumann, and to the committee who organize the Jesup Lectures, I can only offer my deepest thanks for all the kindnesses and considerations they have shown me.

Authors, editors, and publishers have been generous in giving me permission to reproduce certain drawings, and I should like to express my gratitude to all of them. The name of the author is under each drawing, and the complete reference to his work is given in Works Cited at the end of the book. For the use of the figures, I have been granted permission by the following: *Acta Scientifica Fennica; Australian Journal of Biological Sciences;* Birkhauser Verlag (Basel), *Experientia;* Company of Biologists (Cambridge), *Journal of Experimental Biology;* Elsevier Publishing Co. (Amsterdam), Frey-Wyssling, 1948; *Faraday Society; Genetics; Journal of Biophysical and Biochemical Cytology;* Masson et Cie (Paris), *Archives d'Anatomie Microscopique;* National Academy of Sciences (Washington), *Proceedings of the National Academy of Sciences;* Pergamon Press (Oxford), Waddington, 1959; Ronald Press (New York), Wettstein, 1959; The Royal Society (London), *Proceedings of The Royal Society (London) B.* and *Philosophical Transactions of The Royal Society of London (B.);* Springer Verlag (Heidelberg), *Zeitschrift für Vererbungslehre, Chromosoma,* and *Die Naturwissenschaften,* Kuhn, 1955.

C.H.W.

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1. The Production of New Substances

THE title, *New Patterns in Genetics and Development,* which I have chosen for the series of lectures on which this book is based, is ambiguous. It implies, in the first place, that we shall be discussing the problem of form and the appearance of definitely shaped masses of tissue arranged in recognizable patterns, which is one of the most striking and at the same time enigmatic phenomena with which the biologist is confronted. But the arising of orderly forms is only one aspect, and one of the most complex aspects, of the whole process of development. It is usually an accompaniment, and often apparently a consequence of changes in the material constitution of the various regions of a developing system. One can hardly discuss new patterns without devoting a good deal of attention to new substances. And here the other interpretation of our ambiguous title becomes relevant. In the last few years, advances in other fields of general biology, particularly in microbiological genetics and in the ultrastructural biology of adult tissues, have given rise to many new patterns of thought which are applicable, in greater or lesser degree, to the problems of development. The aim of this book is to consider the origin of new patterns of structure in developing cells and tissues in the light of these new patterns of thought.

The changes undergone by developing systems are often spoken of as "differentiation." This is a portmanteau term, and confusion often arises from failure to distinguish the several different types of change which are all included within it; a statement, which may be quite true when one of these is meant, may be nonsense if the word is interpreted in one of its other senses. Differentiation, of course, is always concerned with the differences between two entities, but the entities may be of many dif-

ferent types. The two major categories are differences between two temporal states of the same entity and the differences between two spatially distinct but contemporaneous entities. We find, for instance, that a given region of an embryo changes from gastrula ectoderm through neural plate to neural tube, and finally, perhaps, to the brain. This is a series of alterations in time; and as the name for this general type of phenomenon, I shall use the word "histogenesis." However, we shall find that while one region of the gastrula ectoderm is changing in this way, another region will develop into neurula epidermis and then into the lens of the eye. The difference between the brain and the lens is a difference between two spatially separate parts. For the arising of such differences, I shall use the expression "regionalization."

The differences which arise during histogenesis and regionalization are, to some extent, differences in chemical composition, which could be ascertained in homogenized samples taken from the various stages and regions. But this is by no means the whole of the story. The embryologist is confronted not simply by chemical substances, but by a whole hierarchy of more complex organized entities, such as subcellular organelles, cells, tissues, and organs, in each of which the material substance has some relatively definite spatial arrangement. We need to agree on some terminology in which these spatial factors can be discussed. I propose using the two well-known terms "morphogenesis" and "pattern formation." I shall use morphogenesis when we are concerned with the assumption of a definite shape by a mass of material which we are treating as being homogeneous, that is to say, without separately distinguished parts. When, for instance, the neural plate rolls up into a neural tube, or when a mass of cartilage molds itself into a femur, we can regard these developments as processes of morphogenesis.

They are, in general, only *interesting* examples of morphogenesis in so far as the shapes are definite, that is to say, precisely, or nearly precisely, repeatable in different instances of the same developing system.

I shall use pattern formation for processes in which we wish to distinguish different spatial parts within the developing system and to discuss their geometrical relations. If, for instance, a mass of cartilage in an embryonic limb develops into a number of condensations, and if we wish to consider the relations between the distal and proximal skeletal ele-

ments, or the number and arrangement of the digits, then we shall be dealing with examples of pattern formation.

The application of these terms—histogenesis, regionalization, morphogenesis, and pattern formation—overlap to some extent. This is inevitable because the terms are required to discuss various aspects of what is essentially a unified process: that of embryonic development. The best instrument of thought we can hope for, at least at the beginning of such a discussion, is not a set of rigidly defined and exclusive terms according to which we have decided in advance the phenomena should be analyzed, but rather a relatively flexible terminology that uses words each of which emphasizes a particular aspect of the subject without totally excluding the other aspects.

The Nature of Developmental Processes

The first step toward a discussion of these processes should be to decide, if possible, on the nature of the basic concepts in terms of which an adequate framework for our thoughts can be formulated. Chemists conduct their arguments in a vocabulary based on the concepts of atom, electron, and quantum; geneticists find their foundation in the mutation-site and the gene. What are the corresponding fundamental concepts in embryology? A reading of what one might call the classic books on modern theories of development—such as Spemann's *Embryonic Development and Induction* (1938), Weiss's *Principles of Development* (1939), Lehmann's *Einführung in die physiologische Embryologie* (1945)—reveals a discussion couched in terms, such as induction, determination, self-differentiation, competence, regulation, individuation. These are essentially operational terms. They describe, with more or less precision, the behaviors of various types of cells or tissue fragments as they have been revealed by experimentation. It is well known, of course, that there are several difficulties in the exact definition of the various terms; but these are probably no more, or no less, damaging to their usefulness than are the similar complications involved in the meticulous use of other generally accepted and operationally defined physiological terms, such as vitamins, hormones, metabolism. Within their legitimate sphere, the classic embryological terms are capable of doing good service. As all

operationally defined terms, they are useful for describing the results of experiments, but are feeble guides, or perhaps even deceptive ones, to the nature of the underlying elements whose properties bring about the processes which the experiments discovered.

What should we take those underlying elements to be? There are, surely, two major clues. In the first place, we know that genes determine the specific nature of many chemical substances, cell types, and organ configurations; and we have every reason to believe that they ultimately control all of them. But, in the second place, the fact that regionalization occurs in the development of nearly all organisms—that in all living things more complex than bacteria (and perhaps even in them also) there are different regions each with its own characteristic specificity—shows that something more than the genes must be involved. This regionalization can usually be traced back to the presence of a number of different types of cytoplasm in the body of the cell from which development starts. Thus, the underlying elements to whose properties we have to look for a penetrating theory of development must be genes interacting with particular types of cytoplasm.

Theories of development based on the interactions of nucleus and cytoplasm go back at least to the days of Boveri. It is only recently, however, that theoretical schemes have been worked out in terms of genes, which we now hold to be the main determinants within the nucleus. In the classic embryological treatises, such as the books mentioned previously, the word "gene" scarcely occurs; and even in such a recent book as the compendious *Analysis of Development* (1955) edited by Willier, Weiss, and Hamburger, the single chapter devoted to genes makes up less than 3 percent of the work. In the 1920s and 1930s, some geneticists —Goldschmidt, Muller, Bridges, Haldane, Garrod, and others—began to be interested in the relation between individual genes and the substances whose specificities they determine, a line of work which has since made such enormous progress. But it was not, I think, until the appearance of my own book *Organisers and Genes* in 1940 that a serious attempt was made to envisage the standard embryological concepts such as competence, induction, determination, in terms of the interactions between groups of genes and their cytoplasmic surroundings. Although among embryologists this interpretation of these concepts is still not generally accepted—at least not in their practice as indicated in books such