Major Problems in Developmental Biology

Current Status of
Some Major Problems in Developmental Biology

The Twenty-Fifth Symposium

The Society for

Developmental Biology

(Formerly The Society for the Study of Development and Growth)

Haverford, Pennsylvania, June 1966

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1965–1966

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Major Problems in Developmental Biology

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Major Problems in Developmental Biology

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The Growth and Development of Developmental Biology

JANE M. OPPENHEIMER

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Introduction

The first symposium on Development and Growth was held in August 1939 (Fig. 1). Six years before, in 1933, Thomas Hunt Morgan, in his earlier years an experimental embryologist, was awarded the Nobel Prize for his discoveries concerning the function of chromosomes in the transmission of heredity; four years before the first symposium, in 1935, Hans Spemann had received the prize for his discovery of the organizer effect in embryonic development. Yet Pontecorvo, in his introduction to "Trends in Genetic Analysis," has stated that: "It is no exaggeration to say that before about 1940 what was known on the nature and mode of genetic specificity—i.e., what was known about chromosomal heredity —was but a series of developments on the theory of the gene" (Pontecorvo, 1958, p. 2). Richard Goldschmidt wrote in the preface to his "Physiological Genetics" in 1938 that: "It is emphasized over and over again by writers of texts and by general speakers [that] we know next to nothing of the action of the hereditary material in controlling development" (Goldschmidt, 1938, p. v).

This introductory paper will shortly attempt to describe some of what Pontecorvo called "the historical landscape" (1958, p. 3) of over twenty-five years ago. Since genetics and the study of development have converged during the intervening quarter-century, together with the study of molecules and macromolecules: of proteins, enzymes, nucleoproteins, and others; of cells and organelles; of metabolic pathways and immune reactions; of microbes and protozoans and fungi; and since their convergence has transformed biology and has carried it to depths hardly dreamed of when this Society first met as a Society in 1940, it may be appropriate to inquire to what degree the Society, and in particular its symposia, may have reflected, or possibly have contributed to, the development of the new biology.

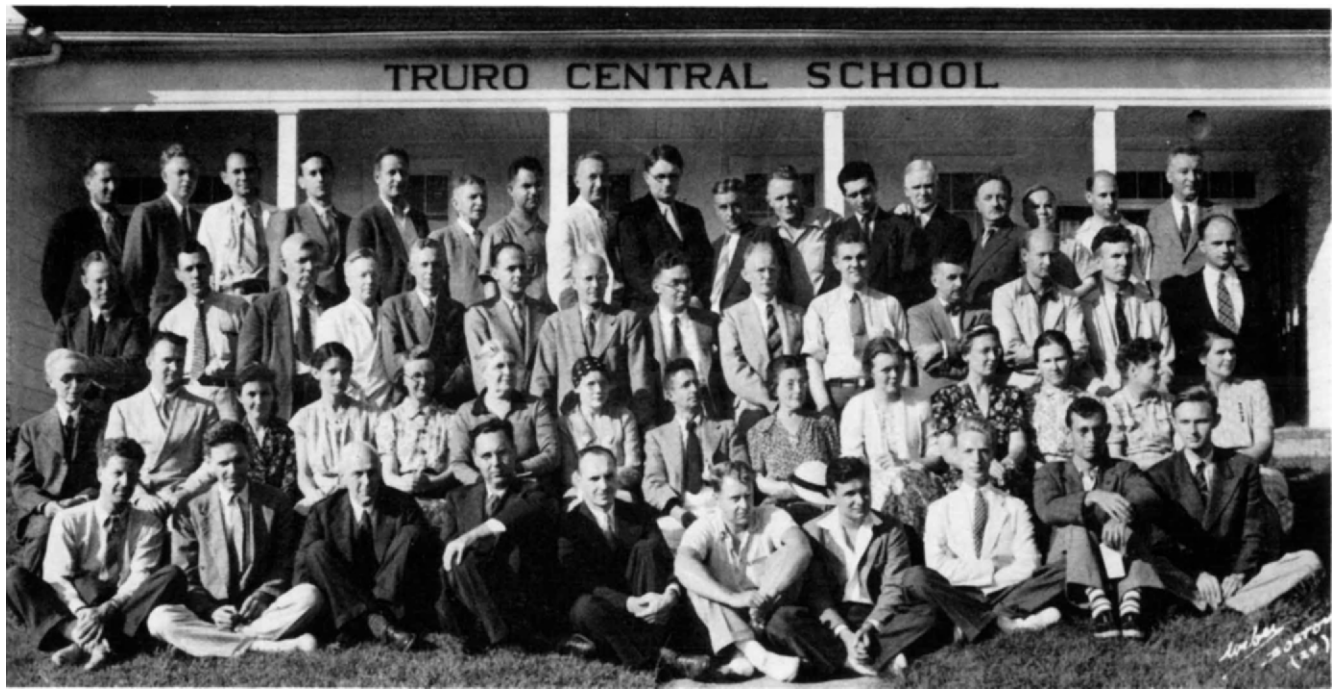
TRURO CENTRAL SCHOOL

FIG. 1. First symposium for Growth and Development, North Truro, Massachusetts, August 7–11, 1939.

Front to back: *First Row, left to right:* Drs. L. C. Dunn, Columbia; V. Hamburger, Washington University; W. H. Lewis, Carnegie Institution; M. G. Brown, Washington University; R. L. Risley, State University of Iowa; L. Walp, Marietta College, Ohio; C. L. Schneider, Harvard; R. S. Childs, Columbia; E. Brill, Harvard; R. Gillette, Washington University.

Second Row: Drs. L. Loeb, Washington University; W. F. Dove, University of Maine; T. B. Steele, Lankenau Hospital Research Institute; Mrs. L. G. Barth; Mrs. J. Needham; Dr. Florence Peebles, Chapman College; Mrs. A. B. Dawson; Dr. F. S. Hammett, Lankenau Hospital Research Institute; Mrs. L. Loeb; K. Hyde, Lankenau Hospital Research Institute; Drs. Louise P. Wilson, Wellesley; Julia Outhouse, University of Illinois; Myrtle McGraw, Columbia; Mrs. Dammann, Columbia.

Third Row: Drs. P. W. Gregory, University of California, Davis; C. Deuber, Yale; H. Dorsey, University of Connecticut; P. White, Rockefeller Institute; E. W. Sinnott, Columbia; P. A. Weiss, University of Chicago; A. B. Dawson, Harvard; R. Grant, McGill University; O. Rahn, Cornell; R. Aronson, Lankenau Hospital Research Institute; H. S. Burr, Yale; C. H. Waddington, Cambridge University; N. J. Berrill and G. H. Sander, McGill University.

Fourth Row: Drs. J. W. Wilson, Brown University; L. B. Clark, Union College; L. G. Barth, Columbia; K. V. Thimann, and L. Hoadley, Harvard; A. D. Mead, Brown University; N. Padis and S. P. Reimann, Lankenau Hospital Research Institute; J. Needham, Cambridge University; O. Glaser, Amherst; G. Toennies and B. Miller, Lankenau Hospital Research Institute; J. F. Daniel, University of California, Berkeley; O. Schotté, Amherst; J. H. Woodger, University of London; C. Stern, University of Rochester; G. Smith, Yale.

Photograph and key kindly supplied by Dr. Paul Weiss

The Greek word *symposium* means *drinking together,* and the equivalent Latin word *convivium,* the German *Gastmahl,* the French *banquet* that resembles our own, all imply that people get together and have a good time; that has been true for members of the Society for the Study of Development and Growth, now the Society for Developmental Biology, since its origin. At a Greek symposium the guests first dined, and then exchanged ideas over wine. In the symposium so vividly described by Plato, the ideas were about Eros; our symposia deal with his fruits. The meetings of what we are in the habit of calling the Growth Society have always been distinguished by a special conviviality. The first seventeen were held in New England, where *Homarus americanus* finds its most favorable environment, and lobster dinners, especially at the North Truro meetings, but often elsewhere too, were particularly felicitous occasions. There used to be music at a Greek symposium, after dining. We had our musician too, of sorts, though with a different tune; none of us who attended the early meetings can forget Walter Wilson's whistle—many decibels of it—when he called us to order. And those of us who were so fortunate as to attend those first meetings remember with pleasure their unhurried pace, now no longer possible in the days of subsidy by governmental agencies, and the generous opportunity for smaller as well as larger groups to exchange ideas in freedom and in leisure.

The pattern for the symposium meetings was set at the first one in North Truro, Massachusetts, where Frederick Hammett, then working in North Truro at the Marine Experimental Station of the Lankenau Hospital Research Institute, expended "tireless efforts for [the] comfort [of those who attended], for their entertainment and for their enjoyment of the sessions" (Hoadley, 1950, p. [261]). The establishment of the Society is bound up historically, in fact, with that of the Lankenau Hospital Research Institute, and also with that of the periodical *Growth,* and these relationships may be briefly examined.

The origins of the Institute, of the journal, and of the Society have been described in a volume of *Growth* dedicated to Hammett at the time of his retirement (Diller, 1950; Hoadley, 1950; Reimann, 1950; White, 1950). Reimann, in his remarks, gave the credit to Hammett for crystallizing the idea of the Institute. According to Reimann, Hammett asked him, "Why don't you try to gather together a few people, try to interest someone in building a laboratory at Lankenau Hospital, and start work on problems of growth and development?" "Growth and development—both normal and abnormal?" I asked, and he nodded

his head vigorously" (Reimann, 1950, p. [255]). It was under the leadership of Hammett, who became scientific director of the Institute in 1927, that the journal *Growth* was established; its first issue appeared in 1937, and Hammett, "as originator of the plan and its mainspring, was to be Editor-in-Chief" (White, 1950, p. [259]); his poor health permitted him to retain this position for a short time only. With all due respect to and gratitude for the very considerable role that Hammett's interest and enthusiasm played in giving impetus to the establishment of the Institute, of the journal, and thus of the Society, we must also remember, with equal gratitude, the tremendous contribution made by Reimann himself, through his own energy and imagination, in designing the symposia and in the early implementation of the plans.

The first symposium on Development and Growth was sponsored by the editors of *Growth,* and it was held in August 1939, at North Truro, as we have said. The meetings were held in the small village schoolhouse; at each session, morning and afternoon for five days, a single talk was the main intellectual sustenance, and the remainder of the time was spent on discussion—what happy days were those! The Society was organized as a result of the success of that first meeting, about whose content more will be said later, and symposia have been held annually since, except during the war years 1943 and 1944, and in 1950 when all members of the Society were invited to attend the Seventh International Congress of Cell Biology that met in New Haven in September. The symposium held in North Truro in 1945 was the only one for which the papers were not published; their titles and authors are, however, listed in a cumulative index included in the fifteenth symposium volume.

The papers delivered at the first ten symposia (minus those given in 1945) appeared, under the able editorship of Irene Corey Diller, in *Growth,* which was from 1941 to 1951 the official organ of the Society, or in supplements to it. The subsequent symposia were published as hardbound books, edited, in turn, by E. J. Boell, Elmer Butler, and for a number of years Dorothea Rudnick, who has found a worthy successor in Michael Locke.

So much, rather formalistic—except for the nostalgic memories of the little schoolhouse and the lobster dinners at North Truro—is factual data reassembled here as an introduction to the main theme of this essay, which is to assay how the content and the nature of the symposia have been related to progress in what we now call developmental biology.

Holding symposia on specialized scientific topics was not a new idea at the end of the 1930's; the Cold Spring Harbor Symposia on Quantitative Biology were in full swing; in fact, one of these, in 1934, had already been devoted to "Some Aspects of Growth," and in 1938 Barth had been the senior author of a paper on the organizer delivered at a Cold Spring Harbor Symposium on proteins (Barth and Graff, 1938). The American Association for the Advancement of Science began to publish symposia in 1938, and the Biological Symposia, edited by Jaques Cattell, began to appear in 1940. What seemed unique about the early Growth Symposia was that they were organized differently from others. When Hammett suggested to Reimann the establishment of an institute to study cancer from a biological point of view he was thinking of bringing to bear on one problem applicable evidence from studies on others; this has often been a successful maneuver in science. It was one of the distinguishing features of the early, as it has been of the later, Growth Symposia that their participants worked in widely divergent disciplines. Never has there been a Growth Symposium without a plant biologist as a speaker; never one without a geneticist, for instance. The diversity of fields covered in the symposia will be further exemplified in a later section of this essay.

The foreword of the first symposium specifies that at that meeting "representatives of the fields of agriculture, bacteriology, biochemistry, biophysics, botany, cytology, embryology, endocrinology, genetics, histology, mathematics, pathology, philosophy, physiology, and zoology concentrated on a single issue, and considerable correlation and conceptual integration was accomplished" (Berrill, 1939, p. [i]). Berrill might have added that representatives from at least two continents presented papers, a situation that was to prevail at an overwhelming majority of the meetings.

The "single issue" Berrill referred to was "Development and Growth," which we should now consider a fairly multiple one. In fact, the papers presented at the first symposium exemplified multiplicity. Warren Lewis, invited to discuss cell division, narrowed his topic to "Some Contributions of Tissue Culture to Development and Growth." Curt Stern and C. H. Waddington separately discussed genes in development, Needham the biochemical aspects of organizer phenomena, Schotté the origin and morphogenetic potencies of regenerates. Sinnott spoke on cell-organ relationships in plants. Two papers on size relationships in growth were delivered by P. W. Gregory and Otto Glaser, respectively. The first symposium, as the second was to do also, concluded with a paper by a real philosopher.

The papers in the first symposium were all rather closely related to what in the old days might have been called embryology. This was not to be true for long. As early as 1940, in the second symposium, every paper dealt with an aspect of what we would call molecular biology (a phrase which, by the way, was already in use in 1939, as we shall see). Although most of the speakers (including the philosopher) addressed themselves to the examination of chemical or physical factors in specific relationship to growth and development, O. L. Sponsler in his talk on proteins, and Rudolph Schoenheimer in his on the synthesis of protoplasmic constituents, made no direct reference to development (at least according to the printed record; only a 3½-page abstract of Schoenheimer's paper was published). Schoenheimer? What was he doing there? His book was not published until the following year. He was surprised himself, I have it on good authority, to have been invited. The reason for his invitation is a clue to the success of the Society: the officers who asked him to come could see the applicability of his work to developmental biology.

The State of Embryology in 1938 and 1939

In order to appreciate the changes in developmental biology that have come about since the Society was founded, and to relate the activities of the Society to these changes, we need to remind ourselves of what investigators of growth and development were thinking about in the late 1930's. It is impossible either to choose or to classify their studies except on a subjective basis, and the investigations to be listed in this and in the following section of this essay have been selected because they seem to me either to look backward or to look forward in an interesting way. Another writer would no doubt choose other examples.

Let us begin with some giants. In 1938 Holtfreter (1938a,b) published the results of the long and exhaustive studies in which he mapped in detail the potentialities of isolated portions of urodele and anuran gastrulae, and the following year (Holtfreter, 1939) his first major discussion of tissue affinity. Harrison published, in 1938, a lecture given the previous year on the multifold accomplishments of the neural crest. Harrison's own method of tissue culture had been useful in the acquisition of some of the results he reported. This technique, in the late 1930's, was beginning to be increasingly exploited by embryologists for the study of embryonic organization. Rudnick in 1938 (1938a,b) studied the differentiation in tissue culture of pieces of the early chick blasto-

derm at the head process and primitive streak stages; Nicholas (1938) cultured 9-day rat embryos in a circulating medium, and Pincus (Pincus and Werthessen, 1938; Pincus, 1939) attempted to study the development of fertilized and artificially activated rabbit eggs *in vitro*. In 1938 Törö reported the homeogenetic induction of neural folds in rat embryos maintained *in vitro;* this was, I believe, the first direct demonstration of neural induction in mammals; lampreys, teleosts, and birds had previously been shown to develop their central nervous tissue in response to inductive stimuli.

Even if all the vertebrates studied resembled each other in developing their nervous systems by induction, the mechanisms of induction were, in 1938 and 1939, as they had previously been and as they still remain, major enigmas.

Chuang, in 1938 and 1939, adduced the first conclusive evidence in favor of inductive specificity on the part of heterogeneous inductors; Toivonen (1938) independently came to similar conclusions. Shen (1939) quantitatively studied a polycyclic hydrocarbon (sodium endosuccinate salt of 1:2:5:6 dibenzanthracene) as an inductive factor, following up work by Waddington (1938) who had demonstrated inductive effects exerted by 1:2:5:6 dibenzanthracene itself. In 1938 Jean Brachet reported on the location of sulfhydrated proteins in developing amphibians; he had studied for four years the respiratory rate of various portions of the amphibian gastrula. In 1939, he discussed the relation of protein and carbohydrate metabolism to the problem of the amphibian organizer (Brachet, 1939).

Boell *et al.* reported in 1939 on anaerobic glycolysis in regions of the amphibian gastrula, and Boell and Poulson (1939) on the respiratory metabolism of normal and genetically deficient *Drosophila* eggs; in 1938 Boell had published a collaborative paper with Bodine on the effect of DNP's on respiratory metabolism during the development of grasshopper embryos (Bodine and Boell, 1938).

Bodenstein (1939) investigated metamorphosis in *Drosophila* by means of interspecific organ transplants; Hadorn and Neel (1938) reported on the hormonal influence of the corpus allatum on pupation in *Drosophila*. In 1939 Hamburger demonstrated sensory and motor hyperplasia in the chick following limb bud transplantation; the previous year (1938), Youngstrom published the first report of the correlation between the appearance of cholinesterase in the embryo and the development of behavior patterns.

Hörstadius, having completed a large number of his isolation and

recombination experiments, reported in 1938 the results of constriction experiments on sea urchin eggs; Lindahl and Öhmann (1938) tried to account for gradients in echinoderm development in metabolic terms. Ries, in 1939, reported the result of pioneering histochemical studies on ooplasmic segregation in a number of invertebrates.

In 1939 White described the growth of excised plant callus *in vitro* in artificial nutrients; the same year Gautheret and Nobécourt in France performed successful culture of undifferentiated plant tissues for potentially unlimited periods. Went, in 1939, reported on the effects of auxin on root formation. English *et al.* (1939) isolated from beans a crystalline substance that showed wound hormone activity. J. R. Raper published in 1939 the first of a series of papers on sexual hormones in *Achlya,* and the same year K. B. Raper (1939; Raper and Smith, 1939) published two papers on conditions favorable for the growth of *Dictyostelium.*

Developmental biologists tend to believe that they are well-supplied with books in the mid-1960's, since new ones appear in frequent succession. A considerable number of books on developmental biology appeared, or were being prepared, during 1938 and 1939, too. The English translation of Spemann's Silliman Lectures on embryonic induction was published in 1938. Dalcq published in English, in 1938, a book on "Form and Causality," and in French, in 1941, a longer one on "L'Oeuf et son Dynamisme Organisateur." In 1939 Paul Weiss published a fine book on "Principles of Development," and his ideas, as expressed in that book, in later talks to the Growth Society, and in papers published elsewhere, were to exert strong influence on the new embryology. The year 1940 saw the appearance of Waddington's "Organisers & Genes" and Windle's "Physiology of the Fetus." Child published in 1941 an 811-page monograph on "Patterns and Problems of Development" in which he considered experimental data to show, as he put it, "that various sorts of gradients which appear in development are manifestations or expressions of underlying physiological differentials of some sort, which are organismic in order of magnitude" (Child, 1941, p. 7). Its length might suggest that its writing had been under way in 1938 and 1939. Gerontology in the later 1960's is supposed to be a modern science; in 1939 Cowdry published the first edition of a 758-page compendium on "Problems of Ageing. Biological and Medical Aspects."

If all these were major interests of embryologists during the late 1930's, what was the state of the sciences then seemingly apart from