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Changing Conceptions of Organization and Induction[1]

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SYNOPSIS. Oscar Hertwig (1896) noted that the central biological problem concerned preformation and epigenesis: which provides the basis for organic development? Does an organism begin preformed and just grow larger, or does form and organization emerge gradually? And how? The best scientific approach to the problem seemed to lie with Wilhelm Roux's program of materialistic experimental developmental mechanics, or "Entwickelungsmechanik." Yet that path did not lead directly to answers. Instead, embryology experienced a cycle of highs and lows throughout the first half of this century, and problems of morphogenesis have often faded into the background, regarded as old-fashioned, descriptive, and nonproductive science.

A century later, morphogenesis has regained a central place within biology. A special issue of *Science* recently reported that "unlike human centenarians who are reaching the end of life, developmental biology is basking in its full-blown prime. Indeed the excitement and promise of the field have never been greater, as researchers close in on the secret of how a single fertilized egg cell goes through the complex and beautifully orchestrated series of changes that create an entire organism" (Baringa, 1994, p. 561).

Despite their centrality to biology's experimental traditions, the pioneering work and research traditions of developmental biology have remained little explored. This project will take up that exploration, analyzing the changing ways central issues of development were addressed earlier this century. Against the background of similar questions, significantly different details in approaches, methods, techniques, and basic assumptions have pushed and pulled researchers in a variety of directions. This paper will focus on the emergence of four research traditions between 1890 and the 1930s, traditions that have waxed and waned in importance since then.

INTRODUCTION

Perhaps the chicken came first and simply transferred its form to the egg, which gave rise to another chicken. Building the form of future chickens into the first solves the fundamental problems of development and morphogenesis. Thus, strict preformationists did not have to worry about development; the inherited form is there and just grows up. For those epigenesists who felt confident that the egg was more important, however, the fundamental problem remained: how does that egg give rise to that chicken? What, in other words, explains morphogenesis? Perhaps the egg is in some causally interesting way "organized" either at the beginning or at very early stages of development. That assumption of organization has provided a useful (or at least comforting) way of thinking through the basic problems of development, though the interpretation and presumed causes of that organization have changed considerably.

Debates about the degree, nature, and significance of organization have recurred in different contexts and with different emphases, but the concern has retained importance. Since the issues surrounding the concept and its meaning and usefulness within science have provoked much debate, examination of the various approaches reveals fundamental differences in the underlying assumptions that influenced the interpretations.

The strength of interest is evident, for ex-

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ample, at the Marine Biological Laboratory in Woods Hole, Massachusetts. "Organization" is a subject listing in the library's old card catalog and contains several dozen works ranging from Charles Manning Child's studies of gradients in 1915 to a symposium volume edited by Conrad H. Waddington in 1957. Not every embryologist used the term or the concept, of course, and others besides embryologists (notably evolutionary paleontologists and morphologists) shared the concern about organization. Yet those embryologists who were concerned with the subject represent lines of research worth careful historical and philosophical attention, and it is on these that I shall focus.

MBL director Charles Otis Whitman (1894, pp. 212, 213) maintained that despite numerous optimistic endorsements of gradual development, no evidence had been presented in favor of the strictly epigenetic view. Rather, "The indubitable fact on which we now build is no bit of inorganic homogeneity, into which organization is to be sprung by a coagulating principle, or cooked in by a *calidum innatum,* or wrought out by a spinning archaeus, but the *ready-formed living germ, with an organization cut directly from a preexisting, parental organization of the same kind.*" By this, Whitman clarified, he did not mean that the exact form of the adult preexists but rather that "there is a primary organization that underlies every anatomical organ" and that determines how development would occur. Organization therefore forms the starting point for morphogenesis, and its study must provide the starting point for embryologists. Yet, as MBL researcher Edmund Beecher Wilson pointed out, it was not clear how Whitman thought this process of organization works or exactly what it is. Defining the nature of that "organization" and how it affects, or at least influences, subsequent development was precisely the core question for embryology.

Wilson (1896, p. 330) explained how the individual cells and parts are coordinated in development to produce a unified and formed organismal whole. This, he felt, was the central biological problem. While he saw much of interest in Whitman's emphasis on structural organization of the developing egg cell, he also found other factors such as germinal localization or extrinsic direction of development potentially promising. Perhaps organization arises not primarily, or not only, in the egg itself but is guided by the nucleus. His own important work on the role of chromosomes during fertilization and cell division suggested that the nuclear material might play a role in guiding or even determining development. In addition, experimental studies showed that the developing organism could respond to changing environmental conditions and was thus not strictly prelocalized. Perhaps some internal organization might also respond in a regulative way to external conditions. The evidence simply remained insufficient to warrant strong conclusions, since "the magnitude of the problem of development, whether ontogenetic or phylogenetic, has been underestimated."

For the leading developmental biologists who accepted the fundamental, causal, analytical and materialistic tenets of Entwickelungsmechanik, the appropriate epistemological approach involved articulating answerable questions and pursuing productive experimental lines of research. Various lines of research thus emerged. Some focused on the presumed preorganization of the cytoplasm or of the nucleus. Others looked to more complex interactions between the embryo and the environmental factors surrounding it, seeking to establish the ways that differentiation occurs and the extent to which it is fixed or flexible at each stage. Still others sought to determine what makes an organism an individual, suggesting that there is something about the organization of the "organism as a whole" that distinguishes it from its surroundings and from non-living phenomena. Progress was measured in small steps, yet researchers sought big theories to explain differentiation. As a result, competing theories and research approaches emerged, each invoking different experimental approaches and using different organisms to support the preferred interpretation.

It is a challenge to organize the apparently diverse contributions to morphogenesis in ways that remain true to the research being done and also provide useful analytical categories for further exploration. Despite the difficulties, developmental views prior to World War II seem usefully to cluster into four dominant sets of shared basic ideas and approaches. These focus on cytoplasmic localization (stressing intrinsic and structural factors), nuclear determination (stressing predetermination and chromosomes), metabolic and chemical organization (stressing intrinsic wholistic factors), and organic regulation (stressing the organic whole and allowing vitalistic considerations). This paper explores the key intellectual factors supporting each of these lines of inquiry with their distinctive research approaches and different set of epistemological assumptions. While this discussion focuses on the emergence of these programs prior to World War II, further research will reveal the fates of each of the four approaches as each re-emerged and has been rearticulated in diverse ways in recent decades with the rise of developmental biology. This short paper will necessarily serve as an introductory outline rather than a final, definitive analysis.

Cytoplasmic Localization

This view was popular around the turn of the century with those holding a primarily morphological emphasis. Numerous studies suggested that the egg in amphibians, sea urchins, chicks, and other organisms experiences very early organization. Apparently the cytoplasm is already differentiated or "organized" in some way so that the egg cytoplasm represents, as Jacques Loeb (1916, pp. 151, 39) put it, "an embryo in the rough." Neither nuclear determinants nor chemical substances produce an organism, Loeb explained, but "a definite arrangement or structure of the material" is required, for "without a structure in the egg to begin with, no formation of a complicated organism is imaginable" (see Pauly, 1987). This puts the emphasis squarely on spatial arrangements and local factors such as the presumed way that the first cleavage lays down the organism's axis, or the way that distinct animal and vegetal regions give rise to different germ layers and ultimately to body parts.

American cell lineagists such as Whitman, Wilson, and Edwin Grant Conklin, who painstakingly traced the lineage of cells in a variety of largely marine organisms through the early cell divisions, saw cytoplasmic localization as a definite factor in directing development. They differed considerably in their conclusions about how much localization occurs and how much fixed direction it offers to subsequent development, a discussion complicated, as Conklin pointed out, because organisms vary in the degree of determination and hence localization. Wilson (1925, pp. 1094, 1117) explained in the third edition of his classic book that research argued for a secondary rather than a primary localization, since organization was not actually predetermined in the egg but arose at a very early stage, as a result of factors within and outside the egg itself. "It is," he wrote, "in any case certain that some features of the prelocalization existing at the time of cleavage begins are the result of an antecedent process of epigenesis." However that localization occurs, Wilson recognized it as essential, "for the inescapable fact remains that the specific reactions of the developing egg *depend upon its organization.*" Yet even in 1925, "Concerning the fundamental nature of this organization we are still ignorant." Years later, John Spangler Nicholas (1949, p. 211) noted that the fundamental problems of organization remained. "It must be admitted," he wrote, that despite years of research, "their final solution has not been attained but we have reason for optimism, for science works slowly but surely toward the solution of any major problem, such as embryonic organization has proved to be."

While tracing cell lineages fell out of favor for about six decades after 1910—since that approach appeared to have yielded what it was going to yield and other, less tedious research approaches emerged—emphasis on cytoplasmic localizations continued. By the 1920s, for example, Walther Vogt had used agar dyes as vital stains to follow the migrations of groups of cells during gastrulation. The result was a series of beautiful "fate maps" that showed the presumed fate of each cell region and that revealed a highly regular and predictable process of cell and germ layer differentiation, though the process did not allow close study of internal cells but only of those on the surface.

The emphasis of those stressing cellular localization (or groups of cells such as germ layers) lay on the early structure and organization of the embryo. This emphasis was reassuring, as it built form into the process quite early without requiring strict preformation and without invoking teleological direction. Researchers tended to focus on early stages of development, to concentrate on selected invertebrates and amphibians that exhibited more determinate rather than less determinate cleavage, and to stress structural and hence morphological considerations more than functional factors. Despite its longevity, this approach lost momentum after 1910 as other lines of research concentrating on later stages and on chemical and other interactive factors appeared more productive and exciting. Only with the 1970s did new research groups again take up cell lineage and cytoplasmic localization as promising in new ways, especially with *C. elegans.*

In stressing cytoplasmic localization, this first group focused on questions about structures, asking: what is the arrangement of different parts in the egg? They asked about localization at any given moment and about the way the patterns of each stage give way to the next by incremental structural changes. The object of knowledge was data about these changes, as they worked to capture the temporal process with a sequence of instantaneous snapshots. The epistemic style, therefore, valued definitive data about local structural patterns. This style of research has also been one of several lines leading to recent productive study of cell movements, for example, or of cell-cell interactions such as those outlined by J. P. Trinkaus (for example, 1966).

NUCLEAR DETERMINATION

In the first decades of this century, those ideas of predetermination focused on the nucleus did not require strictly hereditary determination. Development and heredity had not been neatly separated, but rather were regarded as overlapping and as both important (Allen, 1985; Maienschein, 1987). Theodor Boveri was a leader for this line of research, though even his best students ultimately moved in other directions and he himself stressed that nuclear determination does not explain *all* of differentiation.

Another major inspiration came from Roux's and Weismann's mosaic theory. Historians of embryology know of Roux's so-called "crucial experiment" on frog blastomeres. With a hot needle, he killed one blastomere after the first cell division and watched the remainder develop into a half frog: not literally a half frog, of course, but as the single blastomere would have developed. Roux articulated from this a complex theory of the mosaic nature of development (Churchill, 1966). As elaborated in parallel to Weismann, who set forth his own theory of the germ plasm, the mosaic theory emphasized the nuclear determination of cell fates (Churchill, 1985). Weismann (1898, pp. 6, 467) noted that "Ontogeny, or the development of the individual, depends therefore on a series of gradual qualitative changes in the nuclear substance of the egg-cell." And "The germ-cell contains at least as many determinants as there are different cells or groups of cells in the fully-formed organism which are capable of being individually determined from the germ onwards." Each cell cleavage therefore divides up the inherited nuclear material, according to this view, so that each cell has different "determinants" to guide its differentiation. Presumably these theoretical determinants reside on the chromosome and hence within the nucleus. They link development with evolution, and they seemed to provide a beautiful causal explanation of cell differentiation and hence morphogenesis: form is inherited, but indirectly. Predetermination replaces strict literal preformation.

The realization that all cells have the same nuclear material, and hence that their division can*not* adequately explain differentiation, dampened enthusiasm for this view among embryologists—including those using cell lineage analysis. The view lacked the key feature embryologists sought, an account of morphogenesis—which required an explanation of differential expression or transcription of inherited genetic material. Only since the 1950s have more productive research programs emerged to translate heredity into development.

The emphasis of those seeking nuclear deterministic accounts of development lay on the material of heredity, notably on the chromosomes. This emphasis also proved reassuring, building the basic material causes of form in from the beginning, even though the form was not actually there yet. The appropriate research, then, asked: what is the nature of the nuclear material and its action? The crucial time was fertilization, when the two parental sets of nuclear material united and began to direct the developmental process. As Boveri (1902) demonstrated, sea urchin eggs proved particularly valuable for such research (Baltzer, 1967). They could be shaken into numerous small pieces, even before fertilization, and some of the pieces could still develop. Thus it was possible to ascertain differential effects of larger and smaller amounts of nuclear material and to assess the relative importance of maternal and paternal contributions. Other studies demonstrated the autonomy of chromosomes and the role of chromosomes in sex determination, for example. The research was exciting and highly suggestive, but not conclusive for the study of development since there was no way further to correlate any particular nuclear material, which lay hidden inside the cells, with any particular morphogenetic result.

There were critics, of course. Some saw limitations of the research program for what they regarded as the main questions. They had different epistemological focuses: looking for different objectives to count as knowledge and relying on different approaches to warrant those knowledge claims. They rejected the underlying assumptions that chromosomes hold sufficient significance, that heredity is conveyed by particles, or that this told anything at all about the central questions of development—namely those of morphogenesis. Thus Morgan (1910), in his important essay on "Chromosomes and Heredity," rejected the whole approach, insisting that preformed particulate determinants of unit characters remained merely hypothetical and unappealing. Later the same year Morgan discovered the famous white-eyed male *Drosophila* fly and adopted a research program exploring the material basis of heredity. Yet as has been often noted, this Nobelist in genetics recognized that the problems of embryology (and of morphogenesis) remained unresolved, that embryology and genetics remained two separate lines of research.

Researchers inclined to look for inherited material determinants worked on other problems than morphogenesis, using different approaches. Molecular biology developed as one approach, while Mendelian genetics offered another. Different methods, emphases, organisms, research questions, and other details characterized each. John Tyler Bonner (1974, pp. 2–3) spoke to this divergence, when he pointed out that developmentalists had largely continued to pursue what they saw as the important questions, namely "the classic problems of embryology in all their elegant complexity." Meanwhile, the molecular biologist in particular had gone off working on his own and "feels now that he has solved the problems of genetics it is time to annihilate the problem of development with the same vigor." Naturally enough, Bonner pointed out, "there has not been an entirely satisfactory meeting of these two minds." Similar sentiments appear throughout the twentieth century as embryologists continue to express some annoyance when others "take over" their subject matter without, it seems to them, understanding the deepest and most important issues.

Metabolic and Chemical Organization

The third group also sought to explain morphogenesis in material terms but saw the organism as more self-differentiating and as essentially epigenetic. While the first two groups emphasized the relatively fixed aspects of early cytoplasmic location or inherited nuclear material respectively, the third looked to interactions and to changes over time. This group stressed metabolic factors, taken to include all aspects of physiological responses. They were looking for something other than preestablished localized form and for ways for the organism to respond to changing conditions. Gradients could play that role, or morphogenetic fields or centers of induction. As Ross Harrison (1926) put it, organisms are aggregates of living matter such that "They are never entirely at rest but are continually adjusting themselves to the outside world with which they are in dynamic equilibrium." Studies of regeneration, transplantation, and the resulting induction thus provided productive lines of research for this group (See Dinsmore, 1991).

In his work on regeneration, Morgan cited the importance of polarity in regenerating organisms. The head almost always regenerates head, after all, and not tail, which suggested some internal organizing factor. As he failed to make progress in uncovering the causes of this organization, however, Morgan moved to other more productive research programs after 1910. He concluded (1901, p. 258) that researchers might be asking the wrong questions and that there might be "other questions to which we can expect an answer." Thus, "If our analysis of the problem of development leads us to the idea of an organization existing in the egg, our next problem is to discover how it acts during development."

Child (1915*a*, 1915*b*, 1941) pursued regeneration vigorously, insisting that nuclear determinants, cytoplasmic localization, vitalism, or any underlying "organization" remained unacceptable, hypothetical preorganizations, beyond the reach of scientific method. Instead, he sought a materialistic, indeed a mechanistic, non-preformationist explanation. Thus, development of the individual must be understood in terms of the dynamic relations between the organic structure and its chemical reactions. Yet, it was not simply chemical action, but a more complex metabolic gradient that guided development. This meant that the individual is not strictly autonomous and not strictly self-determining, but responsive. The gradients set up linear, or axial, paths of differential "influence" and could have chemical effects, but were not simply different concentrations of chemicals. Though not always clear exactly what he meant, Child's lengthy books show that he recognized aspects of the physiological complexity of development that many of his contemporaries either missed or did not wish to acknowledge.

Others carried out transplantation experiments. Rather than chopping off parts of organisms to assess how, whether, and under what conditions the parts regenerate, the transplanters transplanted pieces of one organism to another. Amphibians provided favorite subjects, in part because they worked well and the transplants "took," in part because of the ready abundance of material, and in large part because it was possible to transplant pieces from related but quite differently pigmented or differently sized species so that the resulting graft proved easy to follow. Limbs and eyes were moved to all manner of strange and unnatural places for the sake of establishing what the transplanted pieces are capable of doing.

The question was: how much of how the piece developed was determined by its parent and how much by the host to which it was relocated? Hermann Braus, Warren Lewis, Harrison, Hans Spemann, and a host of others joined this study, which concentrated on later stages of embryonic development and assumed that physiological responses play essential roles in morphogenesis. They assumed that development is too complex to observe directly and that experimental disruptions of normal development would provide the most promising ways to achieve useful information. Spemann pursued this work in terms of "fields," which are essentially two-dimensional gradients. Others interpreted the phenomena in terms such as crystals or fabrics, as Donna Haraway (1976) has explained. Julian Huxley and Gavin de Beer in *Elements of Experimental Embryology* (1934) do a fine job of laying out the various gradient and field interpretations in a sympathetic light. As they see it, it was Child, with his gradient interpretation, who showed how differentiation might occur and form might emerge in an epigenetic way. It remained for others to work out that mechanism, and Spemann took the lead.

Spemann extended transplantation studies with his experiments with Hilda (Proscholdt) Mangold which suggested that some part of the developing organism, when transplanted, was capable of inducing development in surrounding tissue. This led to the concept of induction and of an inducer, namely the "organizer." Spemann said that he did "not wish to devise hypotheses as long as exact knowledge is attainable by experimental work," and that the experimental biologist must work carefully, "like the archeologist who pieces together the fragments of a lovely thing which are alone left to him. As he proceeds, fragment by fragment, he is guided by a conviction that these fragments are parts of a whole which, however, he does not yet know." He must work as an artist to master the whole, and he must not jump ahead prematurely or he will not "ultimately achieve a true restoration of the master's creation." Therefore, Spemann (1938, pp. 367–368) insisted, he never articulated an "organizer theory." Rather, the organizer remained a preliminary concept, in need of interpretation and careful crafting (Hamburger, 1988; Horder, *et al.,* 1985).

Spemann's concept initiated a "gold rush" for study of development. Joseph Needham (1930; 1942) led the rich and productive search for the chemical nature of the organizer, while others sought the "organizing principle." Spemann insisted that a "dead organizer' is a contradiction," but others experimented with both living and killed tissue, then also with inert matter to assess what it was that was causing the induction process. Why did the particular part, like eyes or limbs, not develop until some "organizer" material was placed next to it? Was the action chemical, mechanical, or some alternative? Johannes Holtfreter (1991), reporting on a pivotal set of experiments from the 1930s, showed clearly that killed tissue did work to induce differentiation. This undercut Spemann's own vitalistic interpretation, of course, and contributed to the eventual disillusionment with the organizer (see Hamburger on Spemann's vitalism, pp. 64–67). As a result of the confusion of varied approaches and interpretations, Harrison (1937) referred in an address at the American Association for the Advancement of Science meeting in 1936 to embryology as experiencing the "Tower of Babel." For several decades, embryologists increasingly gave up on induction along with the organizer, a fact that Holtfreter especially lamented since he saw induction as a central factor in differentiation in at least many organisms, if not in all.

Those who adopted this third approach faced challenges. While Child's gradients and Spemann's fields, and then organizer, provided ways of thinking about how morphogenesis might occur, the experimental research programs studying regeneration and transplantation did not quickly produce clear answers. Indeed, in the 1930s more questions than answers seemed to emerge with each new experiment. Yet this way of thinking has persisted. As embryology underwent redefinition in the 1950s and 1960s in terms of "developmental biology," and as study of gene expression and the feedback systems (which allow genetic material to inform but not absolutely dictate development) have progressed, this third set of metabolically-oriented research traditions has begun increasingly to merge with—or at least to converge toward—aspects of the other research clusters and styles. Notably, researchers began in the 1950s to explore the concept that the gene might serve as an organizer and promote induction (Locke, 1966). The ways in which the separate lines of research transformed in recent decades remain to be explored.

Organic Regulation

This line of thinking is more problematic and elusive. It overlaps with the previous one, and indeed some of the key figures moved back and forth during their lifetimes in response to their most recent research successes or frustrations. The central idea that calls for distinguishing this approach resides in its emphasis on wholeness of the organism. Development may depend entirely on material factors, but it need not; thus vitalism is explicitly allowed, though it is not required. Paul Weiss (1968) fits here, stressing the interdependence of parts of the whole organism. So, clearly, does William Emerson Ritter (1919) or philosopher Joseph Henry Woodger (1929, pp. 289–325), and the biologists he inspired sound like true believers, insisting on the fundamental organic wholeness of the organism. Edward Stuart Russell (1946) called for scientific study of "directiveness" and "creativeness" in biology, for example, urging that it is the organic rather than the mechanical that defines life and that must be the focus of biological research.

The primary motivation here resides in the underlying assumption that conglomerations of physical and chemical material alone, no matter how structurally or chemically "organized," cannot explain the complex process of differentiation and development of form. These researchers looked to other interpretations of the organic and often saw direction, or what were fundamentally teleological factors or emergent properties or processes, somehow operating to insure proper development. This approach is very promising in the short run, since it addresses how morphogenesis can possibly occur. Yet it relies on problematic and often untestable assumptions and seems to cut off the possibility of future scientific study. How can one study Driesch's hypothetical "entelechies" or Russell's directiveness, or the action of psychic energies that others invoked? For those who endorsed the basic epistemological assumption that we should be seeking clear answers in materialistic terms, experimentally derived and analytically researchable, such organicist programs did not appear truly and properly scientific. The fact that some of the advocates such as Hans Driesch had been accepted members of the experimental corps before they "defected" to embrace "speculative metaphysics" nonetheless makes their changing assumptions and reactions to them informative. Thus, we need further careful study of this fourth cluster to assess its relation to the others and its role for the scientific study of moprhogenesis.

CONCLUSION

We see that competing epistemological styles, or sets of assumptions about the goals and methods of science, have created clusters of fundamental convictions that have yielded different research programs. This paper has just begun to suggest the outlines of each program and to glance at some of the contributions. The challenge remains to study each of the groups in detail, to determine the extent to which the apparently distinct styles persist or undergo transformation over time and against the background of changing research problems and personnel. This goal takes on increasing importance as morphogenesis regains its primacy of place within biology.

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