DEVELOPMENTAL DYNAMICS 219:1–9 (2000)

REVIEWS

A PEER REVIEWED FORUM

Embracing Complexity: Organicism for the 21st Century

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ABSTRACT **Organicism (materialistic holism) has provided the philosophical underpinnings for embryology since the time of Kant. It had influenced the founders of developmental mechanics, and the importance of organicism to embryology was explicitly recognized by such figures as O. Hertwig, H. Spemann, R. Harrison, A. M. Dalq, J. Needham, and C. H. Waddington. Many of the principles of organicism remain in contemporary developmental biology, but they are rarely defined as such. A combination of genetic reductionism and the adoption of holism by unscientific communities has led to the devaluation of organicism as a fruitful heuristic for research. This essay attempts to define organicism, provide a brief history of its importance to experimental embryology, outline some sociologically based reasons for its decline, and document its value in contemporary developmental biology. Based on principles or organicism, developmental biology should become a science of emerging complexity. However, this does mean that some of us will have to learn calculus.** © 2000 Wiley-Liss, Inc.

Key words: organicism; holism; philosophy; history; emergence; computation; development; developmental biology; embryology; organ development; pattern formation; morphogenesis; genes; genetics; molecular biology; genome; complexity; emergent properties; reductionism

WHAT ARE (W)HOLISM AND ORGANICISM?

Bottom-Up and Top-Down Explanations

Imagine a philosophy claiming that the entire physical universe operates solely according to the interactions of matter and energy. No "vital forces" exist, and all living phenomena consist only of chemical and physical processes. Such an ontologic position (i.e., a stance as to what exists in the universe) is called *materialism*, and it provides the basis for contemporary natural science. Then imagine a materialistic philosophy that claims that all complex entities (including proteins, cells, organisms, ecosystems) can be completely explained by the properties of their component parts. Such an epistemological position is called *reductionism*, and it is the basis for most of physics and chemistry, and much of biology (Sarkar, 1998). In addition to its role as a view of how the universe is structured (i.e., as an ontology), reductionism also provides an epistemology and methodology (a way of obtaining and organizing knowledge). In the reductionist epistemology of science, chemistry and biology are not ultimately independent disciplines, because they will eventually have all their explanations "reduced" to the terms of physics. The reductionist epistemology and methodology is strictly analytical. By finding the parts that construct the whole, we will learn and explain everything about the whole, including how it functions. Biological functions of a system will be explained solely in terms of the chemical properties of its parts, and these chemical properties will, in turn, be explained by the physical properties of even smaller parts.[1]

Let us imagine, though, another (ontologically) materialistic philosophy. Here, complex wholes are inherently greater than the sum of their parts in the sense that the properties of each part are dependent upon the context of the part within the whole in which they operate. Thus, when we try to explain how the whole system behaves, we have to talk about the context of the whole and cannot get away talking only about the parts. This philosophical stance is variously called *wholism*, *holism*, or *organicism*. Here, it will be called organicism, because holism is sometimes taken to include nonmaterialistic philosophies such as *vitalism*. In vitalism, living matter is ontologically greater than the sum of its parts because of some life force ("entelechy," "*elan vital*," "*vis essentialis*," etc.) which is added to or infused into the chemical parts. Organicism rejects such a nonmaterialist claim. The difference between organicism and reductionism is that organicism holds that explanation cannot proceed solely from the

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Received 20 March 2000; Accepted 3 June 2000

[1] By "function" we mean the type of physiological behavior that is seen in all biological systems. We are not using the narrower sense of "function," which requires them to enhance reproductive fitness.

properties of fully individuated parts even though all properties of the whole are determined by the properties of the parts. Another way of depicting this disagreement is to picture reductionism as a system where a "bottom-up" approach (e.g., atoms to molecules to organelles to cells to tissues) is sufficient to explain all phenomena. Organicism claims that this is not sufficient and that top-down and bottom-up approaches must both be used to explain phenomena. For instance, reductionistic ontology and explanations would see a tissue as an organized collection of cells and cells as an organized collection of organelles, etc. Organicist ontology and explanations would include those bottom-up considerations but would also include the functioning of the tissue within the organism, the functioning of the organism within its environment (and, perhaps, other parameters as well). The structure and function of a hepatocyte depends not only on the properties of organelles comprising it, but also on the properties of the organ in which it resides. This is not meant as a metaphor, but as a mechanistic property (see for instance, Steuli et al., 1991; Notenboom et al., 1996). The properties of any level depend both on the properties of the parts "beneath" them and the properties of the whole into which they are assembled.

Emergent Properties

One of the principles of organicism is that the properties at one level of complexity (for instance, tissues) cannot be ascribed directly to their component parts but arise only because of the interactions among the parts. Such properties that are not those of any part but that arise through the interactions of parts are called *emergent properties*. For instance, one cannot isolate a molecule and say that it has a temperature. However, a collection of molecules has a temperature. Similarly, semipermeability is a property that cannot be attributed to individual molecules. Nevertheless, membranes built from these molecules can have the property of semipermeability. Searle (1992), in asserting the importance of emergent properties in the nervous system, notes that "just as one cannot reach into a glass of water and pick out a molecule and say 'This one is wet,' so, one cannot point to a single synapse or neuron in the brain and say 'This one is thinking about my grandmother.'" As far as we know anything about it, thoughts about grandmothers occur at a much higher level than that of the single neuron or synapse, just as liquidity occurs at a much higher level than that of single molecules." Thus, consciousness is an emergent higher level phenomena of the system that is made up of the lower-level neuronal elements. Not all emergent properties, lead to organicism. The whole is greater than the parts when these emergent properties cannot be explained solely by using properties that can directly be attributed to individuated parts.

Language provides an excellent analogy by which organicism can be understood (Collier, 1985). Certain combinations of letters form words, and certain organizations of words form sentences. The meaning of the sentence obviously depends on its components words (the parts define the whole). But the meaning of the *words* is often defined by the meaning of the entire *sentence* (the whole defining the part). The following three sentences should illustrate this : (1) The party leaders were split on the platform; (2) The disc jockey discovered a black rock star; and (3) (for baseball fans) The pitcher was driven home on a sacrifice fly. The meaning of the sentence is obviously determined by the meaning of the words; but the meaning of each word is determined by context of the sentence it is in. Parts determine wholes; wholes determine their parts in the sense of allowing properties to be defined. In embryology, we are constantly aware of the parts being determined by their context within the whole. Indeed, this was enunciated clearly by Spemann (1943) when he said that "We are standing and walking with parts of our body which could have been used for thinking had they developed in another part of the embryo."

In our linguistic metaphor, emergent properties can be seen in the relationship of letters to words. The letters, themselves, usually have no intrinsic meaning. But when they are grouped together in certain arrangements (for which certain rules exist), meaningful words emerge. In biology, one often encounters these emergent properties. One of us (S.F.G.) once isolated a monoclonal antibody that bound to and neutralized Sabin type I poliovirus. However, when we tried to find which viral protein was bound by this antibody, the results were frustrating. It bound to none of the individual viral proteins. Eventually, it was determined that the antibodies bound VP1, but only after VP1 had combined with other virion proteins and a conformational change was effected (Icenogle et al., 1981). The neutralizing antibody to poliovirus bound to an "emergent" epitope. Similarly, in renal development, the nephron is formed by interactions between the ureteric bud and the metanephrogenic mesenchyme. If one cultures these tissues separately, neither develops any portion of the kidney. However, if you place these tissues together, the mesenchyme cells form the 10 cell types characteristic of the renal filtration apparatus, whereas the ureteric bud tissue branches as it would have in the intact organism. Ten new cell types "emerged" from the interactions between two cell types, neither of which had any of the specific properties of the proximal convoluted tubule cells, juxtaglomerular cells, or Bowman's capsule cells. Moreover, the shape of the filtration apparatus, with the tubules descending into Henle's loop before ascending into the glomerulus, the connection between the nephron and the collecting duct, the histotypic arrays of the nephrons and their relationship to the collecting ducts are all higher order properties that are reproducibly seen from kidney to kidney. Yet, none is a property predicted from the properties of the isolated metanephrogenic mesenchyme cells or the ureteric bud.

Although some biologists are willing to see the emergent properties as phenomena that involve *unpredicted* aspects of matter, other scientists are even willing to say that such emergent properties *cannot be predicted*. Mayr (1988), for instance, has said, the characteristics of living wholes "cannot be deduced (even in theory) from the most complete knowledge of the components, new characteristics of the whole emerge that could not have been predicted from a knowledge of the constituents." Here, Mayr has in mind the philosophical view that explanations consist of deductions from known laws (Hempel, 1964). If we relax this view, because there are few "laws" in biology, and allow other forms of explanations, properties are emergent if their presence cannot be *explained* from the properties of individuated parts. Note that this is a much stronger claim than that they cannot be predicted: we can explain a lot that we could not have predicted—think of evolutionary history.

Level-Specific Laws

Von Bertalanffy (1933, 1952) saw organicism within biology as having three major components: an appreciation of wholeness through regulation, the notion that each whole was a dynamic, changing, assemblage of interacting parts, and the idea that there were laws appropriate for each level of organization (from atoms to ecosystems). Bertalanffy's third component of organicism follows from emergent properties. This is the notion that different laws are appropriate for each level. Returning to our linguistic analogy, just as laws at one level mandate that only certain letters can make words, laws at another level mandate which words can make a sentence. Parts are organized into wholes, and these wholes are often components of larger wholes. Moreover, when at each biological level there are appropriate rules, one cannot necessarily "reduce" all the properties of body tissues to atomic phenomena. When you have an entity as complex as the cell, the fact that quarks have certain spins is irrelevant. This is not to say that each level is independent of the lower one. To the contrary, laws at a level may be almost deterministically dependent on those at lower levels; but they may also be dependent on levels "above." Harrison was firm on this point, noting that there were "integrative levels" of organization in the embryo and that one could not homogenize these levels. For Joseph Needham, Ludwig von Bertalanffy, J. H. Woodger, and Michael Polanyi, level-specific rules were critical. Needham (1943) wrote: "The deadlock [between mechanism and vitalism] is overcome when it is realized that every level of organization has its own regularities and principles, not reducible to those appropriate to lower levels of organization, nor applicable to higher levels, but at the same time in no way inscrutable or immune from scientific analysis and comprehension." The importance of level-specific rules to our conception of reality has been emphasized by philosophers and has been well summarized by Dyke (1988) and Wimsatt (1995), and the notion of level-specific interactive modules forms the basis of many new computer programs.

HOW HAS ORGANICISM FUNCTIONED IN EMBRYOLOGY?

Organicism has traditionally been the philosophy of the embryologist. Dalcq (1951), for instance, concludes an essay by "asserting his scientific faith in Organicism, which reconciles the struggle for objectivity with a full respect for life." In embryology, organicism has tried to reconcile (ontological) materialism with the observations of (epistemological) emergence; in this sense, it has attempted to seek a middle ground between vitalism and reductionism (see Needham, 1930; Dalcq, 1951; Haraway, 1976; Abir-Am, 1991). Lenoir (1982) has argued that the founders of modern embryology—Dollinger, Pander, von Baer, and Rathke—subscribed to the organicism set forth in Kant's *Critique of Judgement* (quoted in Lenoir, 1982). Said Kant: "The first principle required for the notion of an object conceived as a natural purpose is that the parts, with respect to both form and being, are only possible through their relationship to the whole . . . Secondly, it is required that the parts bind themselves mutually into the unity of a whole in such a way that they are mutually cause and effect of one another."

Such integration was crucial for the embryology of the nineteenth and early twentieth century. Moreover, it survived the transition from descriptive embryology to developmental mechanics. The experimentalists were just as organicist as von Baer and Müller. Indeed, the earlier example of kidney development serves as a convenient illustration of just how well this ontology encompasses experimental embryology. Such experiments on regulation confirmed the phenomena of organicism and emergent properties. (As Cassirer [1950] noted, Roux had attempted to propound a reductionist embryology, but the phenomena of regulation as demonstrated by Driesch put a quick end to this program). Hertwig, one of the leaders of the new experimental school, proposed organicism as the true middle-ground between reductionism and vitalism. He claimed explicitly that "The parts of the organism develop in relation to each other, that is, the development of the part is dependent on the development of the whole." Whitman was so firm a believer in the properties of the whole that he did not believe the cell theory extended to embryos, and Lillie (1906), his student and successor at the University of Chicago and at Woods Hole, confirmed that "the organism is primary, not secondary; it is an individual, not by virtue of the cooperation of countless lesser individuals, but an individual that produces these lesser individualities on which its full expression depends."

Between the World Wars, organicism provided the framework for the embryology of both Europe and the

United States (see Haraway, 1976; Gilbert and Faber, 1996). In the United States, Paul Weiss was most insistent on the importance of the organized whole. In his summary of the case against reductionism (Weiss, 1968), he would assert, “The true test of a reductionist system is whether or not an ordered unitary system. . .can, after decomposition into a disorderly pile of its constituent parts, resurrect itself from the shambles by virtue solely of the properties inherent in the isolated pieces.” He would illustrate this case against reductionism by showing slides of a chick embryo, a homogenized chick embryo, and a chick embryo homogenate that had been stratified by centrifugation. The task of reductionism, he would write, was to have the chick emerge from the homogenate. Weiss saw nothing magical about emergent properties. Rather, he wrote (Weiss, 1955), “Whenever we study such emergent order, we recognize it to be of tripartite origin, involving (1) elements with an inner order, (2) their orderly interactions, and (3) an environment fit to sustain their ordered group behavior.”

One of the most sophisticated notions of organicism can be found in Harrison’s work (1918, 1969; see Haraway, 1976). Harrison rejected the holisms of his day (which privileged the whole and subjugated the parts), seeing a more integrative “whole.” “It is impossible to develop science wholly from the top down or from the bottom up. The investigator enters where he can gain a foothold by whatever means may be available.” Harrison’s foothold was the organ, in particular, the limb. He showed that the limb develops as a “harmonious equipotential system,” just like Driesch’s sea urchin eggs. But whereas Driesch linked this to vitalism, Harrison saw the importance of gradients, morphogenetic fields, and the organization of matter. Similarly, to understand renal development, one not only has to understand the paracrine factors and their receptor mediating these interactions (i.e., the cellular levels below), one also has to understand the placement of the kidneys within the entire developing body, such that the capillaries enter the glomerulus and the collecting ducts are drained by the ureters and enter into the bladder (i.e., the organismal levels above). Organicism not only provided the framework for the experimental embryology of the likes of Harrison, Weiss, Needham, Waddington, Spemann, Dalcq, and Child, it also was confirmed by the experiments of Saunders, Grobstein, and numerous others. Organicism was not built bottom-up from theory, it was built top-down from observation. The robustness of the embryo, its ability to regulate, and its ability to form new structures when different regions were combined were the reasons to assert organicism. It was clearly seen as the alternative to both vitalism and reductionist mechanism.

SO WHAT’S WRONG WITH ORGANICISM?

Bad Company

With so many good embryologists framing their work in organicist terms, why does organicism have such a bad reputation? Why does “concern with the organism as a whole. . . come in more recent decades to be associated with fuzzy thinking and sloppy vitalism” (Maienschein, 1991)? One contemporary embryologist, Lewis Wolpert, is reported as saying (Blakeslee, 1997) “the notion that so-called emergent properties are required for understanding living organisms is ‘a bunch of yak, all talk and nothing more.’ ”Why should some scientists be so hostile to organicism and emergent properties? Such a question is not a “scientific” or a “historical” question, but a “sociological” one. The rules of evidence shift a bit, as we try to make sense of history in terms of social interactions.

The first and most obvious problem with organicism is that it has kept very bad company. Extremely bad company! First, it was often associated with (and confused with) that other holist philosophy, vitalism. In embryology, vitalism has its most famous exemplar in the figure of Hans Driesch. Driesch had hoped to provide experimental evidence for the reductionist mechanism of development. His colleague, Wilhelm Roux had shown that if he destroyed half of a two-cell embryo with a hot needle, the other half developed into a half-embryo, just like a well-developed machine. But Roux’s experiment was incomplete. He had not separated the first two cells. So Driesch, by using sea urchin embryos, did the separation of the first two- and four-cells of the organism. To his astonishment, each of the four cells could become an entire larvae. He eventually believed that these and other manifestations of regulation were not compatible with a materialistic mechanism. In 1899, he wrote a monograph claiming that the embryo contained a vital force, an entelechy, that molded the embryo according to the needs of the situation. He abandoned experimental science (and, thus, is seen as the model of an apostate by developmental biologists) to propagandize his vitalist beliefs (1905, 1908, 1921). Other biologists such as Jakob von Uexküll, agreed with Driesch’s vitalistic embryology and expanded it to include the mind. While other embryologists, such as Oskar Hertwig, were attempting to explain regulation in a materialist, organicist manner, they were drowned out by Driesch and von Uexküll. Indeed, scientists and philosophers had made a severe distinction. One was either a reductionist or a vitalist. Beckner (1967) maintains that it was only toward the middle of the twentieth century that it becomes possible to distinguish organicism from vitalism.

If this association were not bad enough, the Nazis espoused holism as a major part of their “Aryan science.” Even though cosmopolitan liberals such as Driesch publicly repudiated the Nazi claims (Driesch was fired from his faculty position for supporting Jewish scientists), the Third Reich saw holism (either of the vitalist or organicist variety) as a counter to the notion of nature as a “machine”. The Jews, they said, were materialists who could not see the wonders of Nature and who were bent on reducing thought, beauty, and love to mechanical terms (see Harrington, 1997). In actual fact, some of the leading organicist scientists, philosophers, and psychologists, were German Jews. However, Volkish holists such as von Uexküll seized organicism and melded it to an anti-Semitic, vitalist holism (Harrington, 1997).

Ironically, communists also claimed organicism as their own. They were probably the first to distinguish organicism from vitalism, seeing vitalism as idealistic nonsense, but identifying organicism as a variant of dialectical materialism. Orthodox dialectical materialism—unlike anything that Marx explicitly wrote—requires emergent laws at every level of organization of matter from atoms to societies. (Marx, presumably, would agree at least on the transition from human individuals to societies but wisely left pseudoscientific speculation to the less rigorous Engels. Marx, after all, was inordinately proud of the fact that he had abandoned philosophy.) This linkage of organicism and dialectical materialism was made explicit in the 1930s and 1940s by left-leaning anti-fascist biologists, especially British embryologists such as Joseph Needham and C. H. Waddington (see Haraway, 1976; Werskey, 1978) and even some evolutionary biologists including Haldane (1939; see also Sarkar, 1992). Although his analysis otherwise made a great deal of sense, Needham (1943) probably did not help his cause by repeatedly quoting (sometimes inaccurately) communist theoreticians such as Engels and Lenin, as well as Soviet ideologues including Zavadowski and Bukharin, as all supporting a nonreductionist organicism.

Even today, the term "holistic" connotes the alternative, the nonstandard, and the flaky. It is often used in New Age rhetoric to describe the spiritualization of matter and life. There is even a "holistic" (their word) embryology textbook (Grossinger, 1986), which discusses gastrulation, neurulation, and organogenesis in terms of cosmic midwifery and the creation of the spiritual universe. "The first three glands are endodermal: the thymus affecting growth leads to a solar personality; the pancreas affecting digestion and assimilation is lunar; and the thyroid governing respiration is mercurial." This is hardly a point in its favor among scientists.

With ideologic friends like these, who needs enemies? The association with such company as vitalism, fascism, communism, and New Age spirituality should be enough to bring down any philosophy. The amazing thing, of course, is that these four philosophies are mutually incompatible. Organicism stands on its own without being associated with any of them.

Going Against the Great Chain of Being

This association with discredited philosophies would be problem enough for accepting organicism, but it has not been the only problem organicism has had to contend with. Two types of reductionism, physical reductionism and genetic reductionism, provide alternative models of reality. According to physical (global) reductionism, all scientific explanations are eventually reducible to those of physics. This "unity of the sciences" approach is very powerful, and it subscribes to a philosophical pattern, "The Great Chain of Being" that has been extremely popular both in science and in the public imagination (Lovejoy, 1942). In this view, the superior sciences are those that have produced laws that are independent of the specific material circumstances. Gravity works whether the matter is an apple or a planet. As described above, organicism calls physical reductionism into question. It claims that each level is semiautonomous. And if every level has its own rules, then the rules of other sciences are not necessarily reducible to the principles of lower levels. So Mayr (1988) argues that, because living beings act as integrated wholes that are greater than the sum of their parts, biology is not reducible to physics. The behavior of birds need not be reduced to atoms for it to be a scientific explanation. Thus, organicism goes directly against a major social and philosophical tendency—the tendency to see physics as the basic science to which all explanations must be brought.[2]

More Than Genes

Still another obstacle for organicism is genocentrism. This is actually related to the last-mentioned obstacle, because geneticists have routinely made the case that the gene is like the physicists' atom and that genetics took biology out of the realm of natural history and made it a "hard" (i.e., physical and mathematical) science. This type of (genocentric) reductionism in analogous but not identical to the type of reductionism that we have been considering in the context of organicism. It is only analogous because, strictly speaking, the genes invoked by genetic reductionism are abstract entities that obey Mendel's algebraic rules (in the case of diploidy) and it does not matter what they are physically made up of (Sarkar, 1998). Nevertheless, the analogy is so strong, that the two types of reductionism, one with the tiniest particles of matter at the base, and the other with the genes as atoms at the base, are often conflated. Consequently, genetic reductionism at least sociologically plays the role of an obstacle for physical organicism. Having, said this, we will ignore this distinction in the rest of this discussion. At this level of analysis it does not matter.

For most of this century, the major project of biology has been to reinterpret living properties as being epiphenomena of genes. The original goal of evolutionary biology was the reconstruction of life's phylogenies—how fish became amphibians, how invertebrates became vertebrates, etc. (Bowler, 1995). By the mid-twentieth century, this was transformed into a science that studied the differential assortment of genes in

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[2] Although several reductionist biologists had their training in physics or engineering, anti-reductionism in molecular biology was also spawned by one of the greatest physicists of the last century, Niels Bohr [Stein, 1958; Sarkar, 1989].

each generation. "The study of mechanisms of evolution falls within the province of population genetics" (Dobzhansky, 1951). Developmental biology became the study of differential gene expression rather than the attempt to identify the rules underlying morphologic form (see Gilbert, 1996; Gilbert et al., 1996). Similarly, animal behavior gave way to sociobiology and behavioral genetics, and all branches of physiology and anatomy were put on a gene-oriented base. Allen (1985) and Roll-Hanson (1978) have argued that genetics has even espoused a reductionist ontology, let alone epistemology. The notion of the "unit-character" collapsed morphology into genes and left development out of the picture entirely (see Newman, 1997). All biological form and function could be reduced to genes. Higher level phenomena such as development and evolution were seen as epiphenomena of the genes (Dawkins, 1976).

Why is genocentrism such a major force in biology (and in our culture in general)? Is a knowledge of genes essential to solving our ecological crises or are we merely rearranging deck chairs on the *Titanic*? Are most of our health problems caused by gene malfunctions? For example, the advertisements in *Newsweek* and *Science* by Agilent Technologies, a biotech company that produces automatic DNA sequencers, explicitly tells scientists and the general public the world that "Most disease is genetic. The faster scientists can sequence DNA, the faster they can pinpoint the causes of disease so cures can be developed." Some cultural theorists have provided interesting perspectives on why the gene is so important. Haraway (1997) hypothesizes that in today's vocabulary, "genome" has replaced "blood" as the stable basis for race and ethnicity. Similarly, Nelkin and Lindee (1995) see the cultural representations of genes as being similar to the Christian concept of soul, i.e, an extract of the body that is the essence of selfhood, determines identity and character, and from which the body can someday be physically resurrected (as in *Jurassic Park*). The gene functions culturally as the unchanging essence, the rock in the storm. Like science, in general, genetics is seen as containing the underlying truth amidst social uncertainty.

THE GENE: A SLIGHTLY REVISIONIST INTERPRETATION

But the gene is not the unmoved mover of the organism. Although the reduction of all biology to genes has occurred on an enormous scale, it is worth noting that new studies in molecular biology can be interpreted as demonstrating the epistemologic case for organicism. Indeed, we would argue that if there is a place to make the argument for organicism, it is at the level of the gene.

There are level-specific rules, and the whole is greater than the sum of its parts even at the level of nucleotides. Not only are the genes made of component nucleotides, but the nucleotides are grouped into functional modules—introns, exons, enhancers, promoters, silencers, etc. These seem to be evolutionarily assortable modules that can make new genes and new types of regulation by their reassortment (Gilbert, 1979; Baron et al., 1991). Just as certain letters cannot go together and make a coherent word, certain combinations of nucleotides will not make a functional gene. (Hence the term "open reading frames" for the sequences that appear to have the necessary conditions for synthesizing a protein).

But we need not look on evolutionary time scales to see this occurring. In immunology, we see this assortment of different modular units occurring as the lymphocytes develop. The genes for the B- and T-cell antigen receptors do not exist in the embryo. Rather, they are constructed as each lymphocyte develops, segments of DNA from different regions of the genome come together to create a gene during the lymphocyte development. Similarly, RNA editing provides another situation where the information encoding a protein for a protein is created rather than inherited. Such editing can be quite extensive, involving hundreds of nucleotides (Koslowsky et al., 1990). In situations such as these, context is all important.

The function of the part depends on its context within the whole. One sees this on several levels involving the gene. First, what a gene "does" depends on its context. The function of a gene or gene product depends on its interactions with other genes and gene products. β-Catenin can be an adhesion protein in the liver or a transcription factor in the skin. Lactate dehydrogenase can be an enzyme in the muscle or a structural crystallin in the eye. Just as Spemann and Harrison noted for the cells of the embryo, the whole determines the function of the parts just as the parts determine the function of the whole. Second, Spemann and Harrison would also concur that the interactions of cells to form embryonic structures takes place within morphogenetic fields. Here, too, we see how important context is. A gene that produces the absence of limbs in one person causes merely the malformation of the thumb in another member of his family (Freire-Maia, 1975). An SRY gene that is wild-type in one strain of mouse is mutant in another (Eicher and Washburn, 1989). The cellular context even determines if a particular DNA sequence is or is not part of the functional gene. Differential RNA splicing data demonstrates that a particular DNA sequence can be an intron in one type of cell and an exon in another. *Drosophila* sex determination is based on introns in female cells being exons in male cells (Baker, 1989). Context-dependency rules even at the level of nucleotides. Parts determine wholes; wholes determine parts.

THE REACTIVE GENOME

The gene is defined both by its component parts and by its context. What makes the genome "special" is that it is the set of elements that becomes transmitted through the gametes. But as Waddington wrote in

1956, genes are not only actors, but they are acted upon. There are two major levels that can regulate a gene. The first is the cellular cytoplasm. Embryologists (going back to Driesch) have known that the cytoplasm regulates the genome just as the genome regulates the cytoplasm. This was emphasized by Waddington (1956) who pointed out that mosaic specification and induction were both predicated on cytoplasmic activation of genes, and he noted examples of cytoplasmic inheritance as well. In the 1960s, John Gurdon's studies of implanted nuclei similarly showed that the stage of the egg cytoplasm governed the division rates and expression capabilities of the nucleus.

The second level that can regulate genes is the environment. Our present model systems have been selected for their ability to grow without specific environmental cues. That is, these are animals that will develop in the laboratory (Bolker, 1995). They have also been selected for the rapid segregation of the germline from the somatic line (Buss, 1987). These types of organisms privilege studies of the genetic control of development and marginalize the top-down approaches. However, ecologists have known for decades that environment can cause dramatic changes in development. Whether an ant larva becomes a queen or a worker depends on the food she is given; whether a wrasse becomes a male or a female fish depends on whether a male already resides in the reef; whether a *Daphnia* develops a large helmet or a small one depends on whether it (or its mother) has been exposed to a predator; whether a *Bicyclus* butterfly has large eyespots or no eyespots depends on the temperature its late instar larva experiences; whether a turtle develops into a male or a female depends upon the temperature during a critical portion of its incubation (see van der Weele, 1999; Gilbert, 2000, for reviews). These "life history strategies" make up a large part of contemporary ecology. However, the proximate causes for most of these changes are unknown. They represent "top-down" regulation wherein the upper level (the environment) selects the phenotype rather than the lower level (the genes). To be sure, both are needed; but the reductionist approach of explaining the phenotype solely from the component parts of the lower levels will not suffice.

PERSPECTIVES

The genetic approach to development was a redirection of embryology from its original concern with morphology and tissue interactions to a focus on differential gene expression (Gilbert, 1991a,b; 1996; Keller, 1995; Strohman, 1997). The earliest programs for experimental embryology focused on environmental changes that could effect development. These programs analysed context-dependent sex determination, the effects of temperature and ions on development, and the adaptation of embryos and larvae to their environments. Experimental embryology at this time was closely linked to ecology and evolution (Nyhart, 1995). At the turn of the last century, developmental mechanics emulated physiology, and experimental embryology was taken indoors. This led to a radical change in both the types of organisms studied and the types of questions asked. Development was seen as being within the organism, and the interactions of cells and tissues were paramount. The third shift in experimental embryology was the genetic approach. Here, development was seen as being predominantly located within the cell. Thus, the past century has seen a two-step decrease in the explanatory levels of development. The first step removed the ecological level and the second step removed the organismal level.

For the past 40 years, we have been focussing on questions that could be answered by the reductionist program of genetics. The bottom-up approach had no reason to consider organicism. The organism was an epiphenomenon of its genes. However, we are now at the point where the bottom-up approach is meeting the top-down approach. Whole organisms and their environmental interactions are becoming studiable (indeed, by the pioneering of molecular techniques), and gene expression patterns are being seen as being controlled both from the bottom-up and from the top-down (see Pieau et al., 1994; Brakefield et al., 1996; Nijhout, 1999). Needham noted that the critical mistake was in thinking that reductionism (a methodology) gave a valid depiction (ontology) of the organism or its development.[3] We can now see that a reductionist epistemology is no longer always appropriate.

Moreover, a reductionist methodology might also have to be reassessed. Emergent properties can now be approached experimentally as well as conceptually, and the time is right to re-assess Bertalanffy and Weiss' work in light of our new computational and biological prowess. Reductionist methodology was required because one could not vary more than one component at a time and keep track of the results. Computers can do this. Other sciences have moved beyond the linear paths and have started to analyze complex, interacting, systems. Bioinformatics, conceived of as the study of upper-level properties of DNA sequences, has already emerged as the theoretical core of post-genomics. High speed computation and Geographical Information Systems (GIS) technology has transformed ecology (Sarkar, manuscript in preparation). However, in developmental biology—one of the birthplaces of complex systems analysis and a field characterized by interacting and emerging systems—compu-

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[3] It is interesting that the first use of the term organicism (or at least one of the earliest uses of the term) is in André Triton's translation of Delange and Goldsmith's (1912) Theories of Evolution. There, organicism (and its exemplars are O. Hertwig, Herbst, Loeb, and the younger Driesch) is seen as holding forth epigenesis and environmental regulation of cell fate against Weismann's genetic reductionism. This distinction between reductionist ontologies and reductionist methodologies has also been brought up recently by Verschuuren (1995).

tational modeling and analysis have not moved far at all.

The reason may be in our education. There is a fascinating history of computer modeling in developmental biology, and much of it is in the organicist tradition. However, the pioneering work of A. Turing, R. Thom, H. Meinhardt, A. Gierer, I. Prigogine, L. A. Segal, J. Bard, S. Kauffman, and others is difficult to understand without mathematical training and some familiarity with computer science. Such mathematical training is not required by most undergraduate biology departments or developmental biology graduate programs (see Jungck, 1997). Moreover, one would have to look very carefully in any of the major developmental biology journals to find a differential equation or any other type of quantitative analysis. We have been having so much fun and getting so much data from our new molecular tools that we are prone to overlook new approaches that may enable us to solve important questions of differentiation and morphogenesis. The combination of microarray and computer technology may finally allow us to have a multivariable developmental biology of the kind that Bertanaffy and Weiss would have appreciated. Already some of the new computational models (such as Behera and Nanjundiah, 1997; Nijhout and Paulsen, 1997; Meinhardt 1998; Root-Bernstein and Bernstein, 1999) have been exceptionally fruitful in analysing the emergence of form and the importance of gene product interactions within pathways. GIS technology is beginning to enter developmental biology and has already begun to provide startling new perspectives on the relationship between gene expression and form (Jernvall and Selänne, 1999; Jernvall and Thesleff, 2000).

Herrmann (1998) has shown that "inherent in the scientific thought of the past centuries has been the resolve to create a representation of reality that is free from complexity." In developmental biology, this has been an important stage of our own development. But Whitehead (1919) probably got it correct when he asserted that the motto of every natural scientist should be: "Seek simplicity and distrust it." If the sciences of the twenty-first century will be characterized by an analysis of complexity, then developmental biology should be at its forefront. Our science should be mature enough to embrace the complexity of developing organisms.

ACKNOWLEDGMENTS

We thank J. Bolker, R. Burian, J. Fallon, C. Galperin, M.S. Lindee, S. Newman, A. Tauber, and P. Taylor for their helpful suggestions; but this essay does not represent a consensus statement among these individuals.

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