DEVELOPMENTAL BIOLOGY 173, 357–372 (1996)
ARTICLE NO. 0032

REVIEW

Resynthesizing Evolutionary and Developmental Biology

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A new and more robust evolutionary synthesis is emerging that attempts to explain macroevolution as well as microevolutionary events. This new synthesis emphasizes three morphological areas of biology that had been marginalized by the Modern Synthesis of genetics and evolution: embryology, macroevolution, and homology. The foundations for this new synthesis have been provided by new findings from developmental genetics and from the reinterpretation of the fossil record. In this nascent synthesis, macroevolutionary questions are not seen as being soluble by population genetics, and the developmental actions of genes involved with growth and cell specification are seen as being critical for the formation of higher taxa. In addition to discovering the remarkable homologies of homeobox genes and their domains of expression, developmental genetics has recently proposed homologies of process that supplement the older homologies of structure. Homologous developmental pathways, such those involving the *wnt* genes, are seen in numerous embryonic processes, and they are seen occurring in discrete regions, the morphogenetic fields. These fields (which exemplify the modular nature of developing embryos) are proposed to mediate between genotype and phenotype. Just as the cell (and not its genome) functions as the unit of organic structure and function, so the morphogenetic field (and not the genes or the cells) is seen as a major unit of ontogeny whose changes bring about changes in evolution.

INTRODUCTION: THE GENETIC REDEFINITION OF EVOLUTION AND THE ECLIPSE OF MACROEVOLUTION AND HOMOLOGY

In 1932, Thomas Hunt Morgan published his famous address on ''The Rise of Genetics.'' Delivered originally at the Sixth International Congress of Genetics at Cornell University, this would become the historical statement of the field by its acknowledged leader. It would also become the model for nearly all subsequent histories of genetics, many of them written by those tracing their lineage to the Fly Room. It came at a defining moment for the rapidly growing field of genetics. Although initially a unified science, genetics and embryology diverged from each other during the 1920s, and by the 1930s, genetics and embryology had their own rules of evidence, their own paradigmatic experiments, their own favored organisms, their own professors, their own journals, and most importantly, their own vocabularies (Allen, 1978; Gilbert, 1978, 1988). In 1926, Morgan had formally separated genetics from embryology. Now he would go further, proclaiming that genetics had superseded embryology and had put order into the study of evolution. Morgan (1932a) contrasted the genetic approach to evolution with that of the ''old school'' of morphology and comparative anatomy. He claimed that ''genetics has made a very important contribution to evolution, especially when it is recalled that it has brought to the subject an exact scientific method of procedure.'' That same year (Morgan, 1932b), he would contend that genetic studies ''furnish us today with ideas for an objective study of evolution in striking contrast to the older speculative method of treating evolution as a problem

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0012-1606/96 $12.00

of history.'' No wonder paleontologists such as W. K. Gregory (1917) had written about ''genetics *versus* paleontology'': Morgan believed that Genetics brought evolutionary biology out of natural history into the domain of science.

In 1937, Morgan's student, Theodosius Dobzhansky, carried this idea further and took the bold step of redefining evolution as changes in gene frequency. Instead of being a phenotypic science analyzing changes in fossil morphology, embryonic structures, or the alterations that make a structure adaptive in a particular environment, evolution became the epiphenomenon of the genetics of populations. The changes in gene frequency inferred by melanotic moth wings or beetle elytra could model how fish gave rise to amphibians. The Modern Synthesis supported population genetics as the major focus of evolutionary science and viewed genetics as ''Darwin's missing evidence'' (Kettlewell, 1959). Thus, evolution could be competely explained by the mutation and separation of genes. Numerous biologists, especially paleontologists and the Soviet school of population biology, had argued against this view. I. A. Filipchenko (1929) coined the terms microevolution and macroevolution and argued that one could not be inferred from the other. Microevolution concerned the origin of varieties and races within species. Macroevolution concerned the origins of higher taxa. Originally, H. F. Osborn (1925), G. G. Simpson, and other American paleontologists did not accept the view that the fossil record could be explained by the accumulation of minute selectable changes over millions of years. But eventually, the Soviet school of population genetics was liquidated, and the American paleontologists retreated into their museums (Adams, 1990). Population genetics became the predominant explanatory mode for evolutionary biology, and by 1951, Dobzhansky could confidently declare, ''Evolution is a change in the genetic composition of populations. The study of mechanisms of evolution falls within the province of population genetics.'' Thus, evolution was seen as a subset of the formal mathematics of population genetics (see Gottlieb, 1992), and there was nothing in evolutionary biology that fell outside of it. One of the major tenets of the Modern Synthesis has been that of extrapolation: the phenomena of macroevolution, the evolution of species and higher taxa, are fully explained by the microevolutionary processes that gives rise to varieties within species. Macroevolution can be reduced to microevolution. That is, the origins of higher taxa can be explained by population genetics.

There were several reasons for the success of the population genetic approach to evolution. First and foremost, it got results. One could not expect to see species or phyletic change over a lifetime, but microevolutionary changes could be observed in the field or in the laboratory. Moreover, unlike most of biology, these results were phrased in the unambiguous language of mathematics. There were also social factors that hastened the hegemony of genetic approaches to evolution over any other. First, the population genetic approach to evolution was readily funded by the Atomic Energy Commission. Whereas most evolutionary studies had difficulty getting funds and students, concerns about the genetic effects of radiation enabled Dobzhansky and others a constant supply of money and graduate students (Beatty, 1994). Second, the linkage of evolution and genetics fit into certain social agendas. As Paul (1988) has shown, Dobzhansky and others viewed the population genetic model of adaptation as undermining the racial and class associations of ''fitness.'' Moreover, there was the threat of Creationism. In the United States, evolution is still so suspect that no National Science Foundation program is designated as ''Evolutionary Biology.'' In the 1930s and 1940s, it was even more suspect. Genetics, however, was (and is) seen as being true and economically important. If evolution were merely ''a change in the genetic composition of a population,'' then evolution is a mathematically proven fact. Evolution is nought but genetics writ large. In the Soviet Union, the same phenomenon occurred in reverse. Official ideology held Darwinism in enormous respect, but Genetics was a suspect bourgois science. By identifying genetics with Darwinism, genetics was allowed to operate (at least for a time) in the Soviet Union (Adams, 1990).

Genetics also provided a mechanism for evolution when no other mechanism was available. If there were a ''Modern Synthesis'' between genetics and evolution, there had to have been some ''*Unmodern* Synthesis'' that it replaced. This Unmodern Synthesis was the notion that evolution was caused by changes in *development*. The syntheses of E. Haeckel, E. Metchnikoff, A. Weismann, W. K. Brooks, and others were that of evolution and *embryology*. Haeckel's Biogenetic Law had superseded all the other developmental syntheses, and by the 1930s, this synthesis had become both racist and scientifically untenable (see Gasman, 1971; Gould, 1977). It was an easy target for both geneticists and embryologists (such as W. Garstang and N. J. Berrill) to destroy. But in the 1930s and 1940s, embryology had nothing new to substitute for this discredited notion. In fact, embryologists were no longer interested in evolution and had separated themselves from evolutionary biology in an attempt to become ''more scientific'', i.e., experimental (Allen, 1978; Maienschein, 1991). Genetics readily filled this vacuum, and the Modern Synthesis substituted genetics for embryology as the motor for evolution. Thus, embryology—which had previously been the ''handmaid'' to evolution (Baldwin, 1902) and which Darwin perceived as his major source of evidence—gave way to genetics.

One obvious and immediate casualty of this replacement was the autonomy of macroevolution. Macroevolution was completely explainable by the processes of microevolution. It had no status of its own. Another casualty of the population genetical approach to evolution was the notion of homology. Homology was popularized by Darwin's major adversary, Richard Owen (1849), who saw homologous structures as representing the same organ in all its variety of forms and functions. It thereby related organisms to one another by particular affinities of structure. The arms and legs in humans were not only *serially homologous* to each other within the organism, but also *specially homologous*

to ''the fore- and hind-limbs of Beasts, the wings and legs in Bats and Birds, and the pectoral fins and ventral fins of fishes.'' (Evolutionary biologists would now call these structures *historically* homologous or *orthologous.*) Indeed, the *general homologous* plan of all vertebrates could be discerned by anatomical studies. Thomas Huxley (1858) emphasized that these homologies were often seen more clearly during developmental stages of these organisms, and Charles Darwin used homologies to indicate common descent (as opposed to Owen's view that they indicated construction on the same rational plan). However, homologies merely offered evidence for the *operation* of evolution. They did not provide a *mechanism* for evolution. Natural selection and sexual selection, the two mechanisms favored by Darwin, were both based on adaptations in organisms within a species competing for reproductive success. Competition would create new forms out of old ones. Evolution depended upon intraspecies *differences* between organisms, not interspecies *similarities.* And genes manifested themselves as differences. Homology—and the construction of phylogenetic trees based on common embryonic structures—seemed old-fashioned and unscientific compared to the mathematical elegance of population genetics.

Indeed, even before the rise of genetics, studies of embryonic homologies were going against the grain of the ''new'' evolutionary biology. This is clearly seen in the Marine Biology Laboratory Lectures of 1898. One of the speakers, embryologist E. B. Wilson, delivered a classic paper on ''Cell lineage and ancestral reminiscences,'' demonstrating that the cleavage of flatworms, molluscs, and annelids all shared a homologous pattern. Thus, a ''gap'' that seemed ''hopelessly wide'' was finally ''bridged.'' He was followed by an equally famous embryologist, F. R. Lillie, who also spoke on molluscan cleavage. However, Lillie discussed deviations in embryonic development which produced selectable adaptations. He argued that ''modern'' evolutionary biology would do better to concentrate on changes that enabled organisms to survive in particular environments than to focus on ancestral homologies that united animals into lines of descent. Homology was moving into the background.

THE GENETIC REDEFINING OF EXPERIMENTAL EMBRYOLOGY: THE ECLIPSE OF THE MORPHOGENETIC FIELD

If evolution became an epiphenomenon or subset of genetics, then a similar change happened to embryology. The story of the dismissal of embryology from the Modern Synthesis has been repeated many times (e.g., Hamburger, 1988; Gottlieb, 1992), but the reasons for this removal remain obscure. We will try to show here that there are several reasons why embryology could not fit into the synthesis and one of them was that its main explanatory entity, the morphogenetic field, was viewed as a threat to the gene as the unit of ontogeny and phylogeny. From the 1920s through the middle of the 1930s, embryology experienced a Renaissance (see Oppenheimer, 1966). This was the age of Spemann's laboratory and the foundations of the Organizer; it was the age of Harrison's demonstration of limb polarity and of Hamburger's and Weiss' studies on neuron growth and specificity; it was the time of Hörstadius' and Childs' gradients, Willier and Rawles' demonstration of the neural crest cell migrations, and Witschi's observations of sex determination and gonad differentiation. Needham, Waddington, and Brachet were constructing a biochemical embryology, and it appeared as if the basis of morphogenesis was going to be discovered. The research program of this optimistic and robust embryology was *Gestaltungsgesetze,* the attempt to discover the laws of ordered form (Needham, 1931). The basic paradigm of embryology, the idea that gave it structure and coherence, was the *morphogenetic field.*

It is difficult to realize how powerful the concept of the morphogenetic field used to be. It was one of those notions that was so powerful as to be assumed rather than continually proven (Oppenheimer, 1966). To Needham (1950), the field gave ''powerful aid to the codification of *Gestaltungsgesetze. . . .*'' The concept of morphogenetic fields within the embryo was postulated by Boveri (1910; see Sander, 1994) and given explicit definition by Alexander Gurwitsch (1910, 1912, 1922), who initially called them *Geschehnsfeld* and *Kraftfeld,* and finally (1922) *Embryonales Feld.* This idea was popularized through the limb transplantation experiments of Harrison (1918; see Haraway, 1976). Harrison demonstrated that the newt neurula contained two discs of cells which could form a forelimb when transplanted to another region of the embryo. Moreover, cells within this field could regulate. If a limb field were cut in half and the two halves transplanted to different locations, each half would form a complete limb. Conversely, if two half-limbs were grafted together in the same orientation, the fields could regulate to form one normal limb. If undetermined cells or tissues were introduced into the field domain, they became organized and incorporated into the limb. Harrison (echoing Driesch) called this a ''self-differentiating equipotential system.'' Harrison's friend, Hans Spemann (1921), reinvented this concept as an *Organisationsfeld* and said that the dorsal blastopore lip established such a ''field of organization.'' Paul Weiss (1923) would come to similar concepts and names (perhaps independently) and he would give this concept an important theoretical basis. These fields designated areas of embryological information, bound by physical substrates. The components of these fields created a web of interactions such that any cell was defined by its position within its respective field.

The morphogenetic field—like the terms homology or gene—meant somewhat different things to different people. This might be expected when the term is applied to systems as diverse as regenerating planaria, neural induction, and limb determination (see Herrmann, 1964). Like an electromagnetic field, the term denoted both informational and regional relationships. Needham (1950) approved of the use

of fields to explain embryonic phenomena, and he combined the views of Spemann, Waddington, and Weiss in the following definition:

> A morphogenetic field is a system of order such that the positions taken up by unstable entities in one part of the system bear a definite relation to the position taken up by other unstable entites in other parts of the system. The field effect is constituted by their several equilibrium positions. A field is bound to a particular substratum from which a dynamic pattern arises. It is heteroaxial and heteropolar, has recognizably distinct districts, and can, like a magnetic field, maintain its pattern when its mass is either reduced or increased. It can fuse with a similar pattern entering with new material if the axial orientation is favorable. The morphogenetic *gradient* is a special limited case of the morphogenetic field.

Paul Weiss' textbook ''Principles of Development'' (1939) popularized the field concept and used it as an organizing principle for all of embryology. Weiss noted that ''the field concept has been extensively adopted by embryologists,'' and he set out to provide some structure to this flexible concept. His concept of the field was based on purely empirical evidence, and he concluded that the field had the attributes of individuality, heteropolarity, and gradation. Moreover, not only did most developmental phenomena show these field properties, but the field had a real, physical, existence. ''The field concept is not only a useful circumlocution, but an expression of *physical reality*.'' This elevated the field to ''the dignity of an *object* of *research*,'' and it imposed a duty to study it just as one would study any newly discovered natural phenomenon. ''If the term field were mistaken for a sort of narcotic devised to appease the mental discomfort arising from our profound ignorance of the problem of organization, its use would be highly inexpedient.''

In addition to Weiss' highly interactive, ecosystem-like fields existed a related model, the *gradient-field*. This was the brainchild of Gavin de Beer and was popularized in Huxley and de Beer's ''Elements of Experimental Embryology'' (1934). Such a gradient-field would combine the morphogenetic field concept with the gradient concept. As De Robertis and co-workers (1991) have noted, this concept had three sources of evidence. First, the was the *Gefäll* (gradient) hypothesis of Boveri, whereby differential concentrations of substances could determine cell fate. Second, there were the experiments of Swett (1923) which showed that the maximum forelimb-forming ability is found in the anterodorsal region of the forelimb field and decreases gradually from there to the rest of the field. Third, experiments on regenerating planaria showed that whether a particular group of cells regenerated a head or a tail depended solely on the cells attached to it. If the cells were at the anterior tip of the amputation, they became head; if they were at the posterior end of the amputation, they became tail. Moreover, if both head and tail were cut off the planarian, whichever cells were anterior formed head; whichever were posterior formed tail. The field-like nature of this phenomenon was shown by making deep cuts into the head region. If prevented from re-fusing, each portion would form a new and complete head. Child (1915, 1941) showed that there was an axial gradient to this regeneration potential. The percentage of animals able to regenerate heads decreased as the distance of the amputation site from the anterior. (Weiss criticized the linkage of fields with gradients. The gradient, he felt, was just a symbol to indicate the direction and rapidity of the decline in field activity.) There were several related, but competing, notions of what exactly a field was.

Then, as Opitz (1985) remarked,

> In one of the most astounding developments in Western scientific history, the gradient-field, or epimorphic field concept, as embodied in normal ontogeny and as studied by experimental embryologists, seems to have simply vanished from the intellectual patrimony of Western biologists.

What destroyed the morphogenetic field? One answer is that nothing destroyed the morphogenetic field. No data were presented arguing that the idea was wrong or that fields did not exist. Rather, the morphogenetic field was eclipsed and ignored. There were several reasons for this eclipse. First, biochemical techniques were not good enough to enable embryologists to examine field phenomena such as limb polarity, neural tube patterning, and so forth. Second, there was the decline of funding for biological sciences in Europe, especially in Germany, which had been the intellectual and institutional base of embryology. Third, there was the rise of genetics with its alternative program for development. This last point is critical, for just as evolution became redefined as the study of changes in gene *frequency*, so embryology became redefined as the science studying changes in gene *expression* (Morgan, 1934). Since morphogenesis was subsumed in the larger category of gene expression, fields were not needed. Eventually, embryogenesis became synonymous with cell differentiation, and by 1948, Sol Spiegelman could argue that cell differentiation was synonymous with differential protein synthesis and could be studied more readily in *Escherichia coli* or yeast than in metazoan embryos. The formation of complex organs could be seen as being caused by small changes in the gene expression, just as the evolutionary alterations of complex morphology could be effected by the accumulation of small gene changes. Thus, two phenotypic sciences, embryology and evolution, were given new, genotypic, definitions (see Gilbert, 1996a).

The Genetics program of biology was in direct opposition to the concept of morphogenetic fields. Morgan, who had once been second only to C. M. Child in his publication record on gradient fields, blocked the attempts of Child and his students to publish their findings. Morgan considered such work old-fashioned and not good science (Mittman and Fausto-Sterling, 1992). Indeed, Mitman and Fausto-Sterling (1992) conclude that Morgan was so adamant about ridiculing the field notion because in the 1930s, *the morphogenetic field was an alternative to the gene as the unit of ontogeny.*

Neither field nor gene had been seen. Both were postulated on the results of experimental data. Both sought to explain inheritance. In planaria, the inherited information could be seen in the gradient which enabled the organism to form a head at one end and a tail at the other. Upon splitting, each half inherited the ability to make a whole and properly organized animal. In *Drosophila*, several generations of flies could inherit a trait according to strict statistical laws, suggesting the involvement of nuclear chromosomes. The gene and the field were in opposition.

The geneticists and the embryologists ridiculed each other's theories. In his aptly titled ''The Rise of Genetics,'' Morgan laments,

> If another branch of zoology that was actively cultivated at the end of the last century had realized its ambitions, it might have been possible to-day to bridge the gap between gene and character, but despite its high-sounding name of *Entwicklungsmechanik* nothing that was really quantitative or mechanistic was forthcoming. Instead, philosophical platitudes were invoked rather than experimentally determined factors. Then, too, experimental embryology ran for a while after false gods that landed it in a maze of metaphysical subtleties.

Geneticists portrayed embryologists were seen as being old-fashioned, mystical, and metaphysical, enemies to good science. Because of these characteristics, they had failed to achieve their goal of linking genes and characters. But this was Morgan's rhetoric; it was never the goal of most embryologists. Embryologists (as R. Goldschmidt noted in 1940) had not been interested in gene expression; they had other problems (induction and morphogenetic fields in the program of *Gestaltungsgesetze*) to keep themselves occupied. Morgan presented no evidence against fields or gradients (see Gilbert, manuscript submitted for publication). Rather, these concepts were viewed as being mystical, holistic, relics of the past, not to be taken seriously in the new gene-based reductionist biology.

Embryologists, on the other hand, saw genetics as ''no more intellectual than...a game of cards.'' Certainly, most embryologists did not feel that they needed to take genes seriously. Embryologist N. J. Berrill (1941) said that he felt that genes were ''statistically significant little devils collectively equivalent to one entelechy.'' Genes are not mentioned in most of the contemporary embryology texts (including Spemann, 1938), and Harrison (1937) could ask how the geneticists could possibly say that genes controlled development when they could not explain how identical genes in each cell created different cell types and when they could not point to any examples of genes being active in early development. Genes could determine the number of bristles on a fly's back, but they could not determine how a fly constructed its back in the first place. The construction of the organism was accomplished by fields. The contempt of embryologists for evolutionary biology also helped write embryology out of the synthesis (see Smocovitis, 1994). They considered embryology as an experimental discipline, superior to the collecting and describing that characterized genetics and evolution.

De Robertis and colleagues (1991) have suggested that morphogenetic fields disappeared from the literature because they were abstract, almost metaphysical, conceits that could only be revealed experimentally. However, at the time, morphogenetic fields were no more abstract than genes, and even geneticists such as Bateson and Goldschmidt admitted that the gene was a metaphysical concept whose physical reality remained in doubt. Oppenheimer (1966) suggests that the field concept died out because its validity was taken so much for granted that nobody set down to prove it. However, we would contend that morphogenetic fields disappeared from the literature because the techniques to analyze them had not yet appeared and because they were eclipsed by the genetic explanation of development in which fields were not needed.

By the late 1930s, evidence was obtained for genetically controlled programs of embryogenesis (Morgan, 1934; Schultz, 1935; Beadle and Ephrussi, 1937), and mutations were found that involved the early stages of animal development (Gluecksohn-Schoenheimer, 1938). The eclipse of the field by the gene had been started. The success of the genetic program is manifest in our being so ignorant of the power that morphogenetic fields had prior to World War II and the rise of Genetics.

THREE RE-DISCOVERIES

The Modern Synthesis is a remarkable achievement. However, starting in the 1970s, many biologists began questioning its adequacy in explaining evolution. Genetics might be adequate for explaining microevolution, but microevolutionary changes in gene frequency were not seen as able to turn a reptile into a mammal or to convert a fish into an amphibian. Microevolution looks at adaptations that concern only the survival of the fittest, not the arrival of the fittest. As Goodwin (1995) points out, ''the origin of species—Darwin's problem—remains unsolved.'' This reexamining of the Modern Synthesis has led to three great *re*-discoveries in modern biology. These are the simultaneous rediscoveries of macroevolution, homology, and the morphogenetic field. A new synthesis is emerging from these three areas, and this developmentally oriented synthesis may soon be able to explain macroevolutionary as well as microevolutionary processes. The first condition for their rediscovery came from scientists such as R. B. Goldschmidt and C. H. Waddington, who saw that all changes important in evolution are alterations in development. When we say that the one-toed horse is derived from a five-toed ancestor, we are saying that changes have occurred in the development of the limb cartilage cells. Some genes involved in chondrocyte growth, placement, or differentiation have changed. Evolution, to use Goldschmidt's (1940) phrase, involves heritable changes of development. This can be represented as follows (Gilbert and Faber, 1996):

$$\text{Functional Biology} = \text{anatomy, physiology, cell biology, gene expression}$$

$$\text{Developmental Biology} = \delta\,[\text{functional biology}]/\delta t$$

$$\text{Evolutionary Biology} = \delta\,[\text{developmental biology}]/\delta t$$

Here, a *tertium quid,* development, has been imposed between Ernst Mayr's two categories of functional and evolutionary biology. This interpositioning is both conceptual and physical. First, it suggests that to go from functional biology to evolutionary biology without considering developmental biology is like going from displacement to acceleration without considering velocity. Second, it positions development as hierarchically between the two other categories and mediating between them. Development not only is the agent through which these changes are effected, but development constrains selection in its ability to produce new phenotypes (Alberch, 1982). Third, it suggests that there might be a physical substrate which accomplishes this mediation. We suggest that the morphogenetic field is such a substrate.

The Rediscovery of Macroevolution

The concept that macroevolution could not be derived from microevolution remained as an underground current in evolutionary theory. Every so often, it was brought to the surface by developmentally oriented evolutionary biologists such as Goldschmidt, Waddington, or de Beer. In 1940, Richard Goldschmidt stated the challenge to those who proposed the Modern Synthesis. How could the origin of such things as mammalian hair, aortic arches, mollusc shells, cnidocysts, or the compound eye be explained ''by accumulation and selection of small mutants''? But these attempts to decouple microevolution from macroevolution were either ignored or marginalized (see Gilbert, 1994a).

Macroevolution was brought back as an autonomous entity only after Eldredge and Gould (1972), Stanley (1979), and others postulated an alternative view to the gradualism that characterized the Modern Synthesis. By 1980, Gould claimed that the idea of ''gradual alleleic substitution as a mode for all evolutionary change'' was effectively dead. This view did not go unchallenged, and by 1982, Gould's view had become more specific. It wasn't that the Modern Synthesis was wrong; rather, it was incomplete. ''Nothing about microevolutionary population genetics, or any other aspect of microevolutionary theory, is wrong or inadequate at its level. . . . But it is not everything'' (Gould, 1982; p. 104). While punctuated equilibrium remained a controversial theory, it did bring to light the question of the autonomy of macroevolution. Indeed, the failure of microevolutionary biology to distinguish between punctuated equilibrium and gradualism demonstrated its weakness when applied to macroevolution (see Ayala, 1983). Molecular studies (King and Wilson, 1975) were similarly pointing to ''evolution at two levels,'' one molecular, the other morphological. Thus, by the early 1980s, numerous paleontologists and evolutionary biologists (Gould, Stanley, Eldredge, Verba, and most critically, Ayala) came to the conclusion that although macroevolutionary phenomena were underlain by microevolutionary phenomena, the two areas were autonomous and that macroevolutionary processes could not be explained solely by microevolutionary events.

The Rediscovery of Homology

Homology is an important word again. Brian K. Hall (1994) has recently published a 13-chapter discussion of its meaning, and David Wake (1995) noted that whatever it means, it is *the* most important concept in contemporary biology:

> Homology is the central concept for *all* biology. Whenever we say that a mammalian hormone is the ''same'' as a fish hormone, that a human sequence is the ''same'' as a sequence in a chimp or a mouse, that a HOX gene is the ''same'' in a mouse, a fruit fly, a frog, and a human—even when we argue that discoveries about a roundworm, a fruit fly, a frog, a mouse, or a chimp have relevance to the human condition—we have made a bold and direct statement about homology.

Homology was rediscovered almost simultaneously by several groups of scientists, including molecular biologists, developmental geneticists, clinical geneticists, and paleontologists. Paleontologists had continually been using the term but dramatically reformulated it in the 1980s (Van Valen, 1982; Roth, 1984; Wagner, 1984), largely as a result of critiques of the adaptationist program in evolutionary biology. Gould, in particular, hit vehemently against the adaptationist paradigms of contemporary evolutionary biology and substituted a paradigm based on developmental constraints and homology. In his paper with Richard Lewontin (1979), ''The Spandrels of San Marco,'' the idea of developmental homology was reasserted, and the ''just-so stories'' of the adaptationists were held up to ridicule. Gould (1977) was able to go a step further than his predecessors by postulating mechanisms that would produce homologous structures and at the same time provide routes for rapid morphological change. These mechanisms were heterochrony (changes in the relative timing of developmental events) and allometry (differential growth of parts). Both these mechanisms had been proposed earlier by developmentally oriented evolutionary biologists (heterochrony by de Beer, 1940; allometry by Huxley, 1932), and Gould uses them to demonstrate how developmental changes can rapidly create macroevolutionary novelty. Indeed, if the Eldredge and Gould and Stanley model of Punctuated Equilibrium were correct, they would need a model of evolution that could create relatively rapid changes. Allometric growth rates could cause the huge antlers of the Irish elk, the single-toed horse, and the remarkable cerebral cortex of *Homo sapiens.* By heterochrony, one could generate de Beer's patterns of neoteny and paedogenesis, which could

generate new and successful phenotypes. Gould's 1977 book is important in exorcising the ghost of Haeckel and allowing development to become part of evolutionary theory again. Moreover, although heterochrony and allometry have proved to be insufficient as mechanism to effect the integration of development and evolution (Raff and Kaufman, 1981; Raff, 1996), it did focus attention on homology. By the 1980s, homology had become reestablished as a major area in paleontology.

The molecular rediscovery of homology was predicated on nucleic acid hybridization and protein sequencing. These techniques showed that there were similarities between protein sequences (such as those in globin) and that nucleic acids also showed regions of similar or identical sequence. Finessing the classic distinction between analogy and homology, Roy Britten (1967) proposed that homology between nucleic acid sequences referred to ''the degree of similarity between the nucleic acid sequences of different species.'' This was best observed when globin gene and protein sequences were compared both within an organism and between organisms. Thus, the human α, β, δ, γA, and γG globins each shared certain sequences, but were different in certain ways. Moreover, between species, the various globins were also similar and the similarity was proportional to the relatedness of the species. Horse and human α globins are distinct, differing in only 17 amino acids of 141. The only difference between human and gorilla α globin occurs at the 23rd amino acid. Since the various globins (and their genes) are similar in structure within the body, they can be said to be *serially* homologous (*paralogous*, to use Fitch's 1970 term). Since they also are similar between species, they would conform to Owen's (1848) notion of ''*special* homology'' (Fitch's *orthologous* category). The *general* homology of globins to one another implies knowledge of the relationship of their structure to a particular function, and the oxygen transport function is seen to be dependent upon particular conserved sequence structures. Indeed, one also finds this homologous structure in the proteins and genes of myoglobin. Thus, as Jukes (1968) put it, ''the genes responsible for the production of the globin portion of the hemoglobins and myoglobins are all derived from a common archetypal piece of DNA, probably containing 486 base pairs.''

Not only does this language harken back to that of Owen, but so does the mechanism for the production of the homologous sequences (Gilbert, 1980). Owen (1848) viewed the archetypal vertebra as undergoing ''vegetative repetition'' to produce a chain of identical vertebrae. Each of these vertebrae could then undergo ''independent modification'' for its offices of existence. According to Britten and Kohne's hypothesis (1968) for the generation of families of related DNA sequences, there would be a nonrepeating ''archetypal''sequence that would undergo ''saltatory replication'' to form a tandem family of identical DNA sequences. Thereafter, these duplicated copies would be free to undergo ''independent mutation'' and be so selected. The molecular biologists at the Carnegie Institute of Washington had rediscovered homology in the DNA.

But the most far reaching rediscovery of homology came in developmental biology. The first series of discoveries came from the study of homeosis. Homeotic traits had been a sidelight of evolutionary theory ever since William Bateson collected them together in 1894. He noted that differences in the number or type of segment represented discontinuous patterns of evolution. In the 1940s, both C. H. Waddington and R. B. Goldschmidt identified mutations whereby one type of insect segment was transformed into another type of segment, and they claimed that these ''homeotic mutants'' might be the key for understanding the relationship between genetics, development, and evolution. In some of these mutants, parts of the antenna were replaced by the homologous part of the leg; e.g., the tip of the antenna was replaced by the claw of the leg. In other mutants, the entire antenna had been replaced by the leg. In some mutants, the balancer (halteres) of the fly had been replaced by wings, causing the di-pteran to resemble a more primitive four-winged insect.

E. B. Lewis (1978, 1985) proposed a hypothesis that brought these mutations to bear on evolution. It was based on a notion of evolution by gene duplication (Ohno, 1970) which, itself, had similarities to the homology theories of Owen. According to Lewis, the second thoracic segment (having both wings and legs) is the evolutionary baseline for the insects. He then proposed that this gene should have undergone several rounds of duplication and that there should be one gene for each segment below the second thoracic level. As each successive gene became active, a new set of structures are formed, distinguishing that segment from any other. In the last segment, all these genes would be active. Mutations in these genes could produce evolutionarily atavistic phenotypes, such as when those mutant genes in the third thoracic segment convert the halteres into wings.

Three major groups (E. B. Lewis and D. S. Hogness in California; W. Gehring in Basel; T. Kaufman in Indiana; and their respective students) used the new molecular techniques to isolate and sequence these genes, and they discovered a remarkably stable region: a 180-bp consensus sequence called the ''homeobox.'' It appeared that the genes responsible for homeotic transformations were themselves homologous. In the 1980s, another advance was made. These same homoeotic genes were found to exist in vertebrates, initially in *Xenopus laevis* and then in mice, humans, birds, and fish. The original paper demonstrating vertebrate homeobox genes (Carrasco *et al.*, 1984) noted that ''if the frog gene cloned here eventually turns out to have functions similar to that of the fruit fly genes, it would represent the first development-controlling gene identified in vertebrates.'' These genes were said to be homologous, and since the homeotic genes appeared to create the anterior–posterior axis in flies, it was speculated that the same genes might create the anterior–posterior axis in humans. To some, this idea seemed bizarre. Vertebrate body segmen-

tation and insect segmentation are thought to be independently evolved modifications. Insects don't have somites or bones. Vertebrates don't have germ bands or cuticles. It seemed that the molecular biologists had forgotten the distinction between homology and analogy. Then, something happened. First, it was shown that the homeotic genes of mice, humans, and other vertebrates are arranged in the same order on the chromosome as the homeotic gene complex in the fly. Second, it was shown that the anterior–posterior expression pattern of the individual genes was the same in the fly and in vertebrates (see McGinnis and Krumlauf, 1992; Krumlauf, 1993; Bachiller *et al.*, 1994). And last, it was shown that the enhancer region of a human homeotic gene, such as *deformed*, can function within *Drosophila* to activate gene expression in the same relative position as in the human embryo—in the head (McGinnis *et al.*, 1990; Malicki *et al.*, 1992).

In the 1990s, the use of homologous recombination to functionally delete homeotic genes in mice enabled numerous laboratories to see what happened when vertebrates lacked one or more of these genes. The results demonstrated that these genes controlled the formation of the anterior–posterior axis in vertebrates as well as in flies and that deletions of these genes could produce atavistic changes such as the formation of reptilan jaw and neck vertebrae in mice (Chisaka and Capecchi, 1991; Rijli *et al.*, 1993). Studies by Gaunt (1994) and by Burke and her colleagues (1995) have shown that the specific expression pattern of these homeotic genes is responsible for forming the identities of the vertebrae along the anterior–posterior axis in amniotes. Indeed, the finding that every animal has similar genes, has them in the same chromosomal order, and uses them to specify the same relative positions along the anterior–posterior axis has caused Jonathan Slack and his colleagues (1993) to go back even farther than Owen, to Étienne Geoffroy St-Hilaire, who felt that all animals were variations on the same general plan of existence. At a particular ''phylotypic'' stage of development, each animal expresses these genes to create the specification of its cells along the anteroposterior axis. This view stresses the similarities of embryonic development across the phyla. Even though insects and vertebrates create their body axes, limbs, and nervous systems in different ways, there appears to be an essential underlying unity operating in the development of every animal on this planet. The comparison of the homeotic gene complex to the Rosetta stone (Riddihough, 1992; Slack and Tannahill, 1992) is apt: Their homologies enable us to translate our knowledge of *Drosophila* development into the unknown realm of vertebrate embryogenesis.

The segmentation of *Drosophila* and the segmentation of vertebrates had been a classic example of analogy. Yet, here it was seen as being directed by a homologous set of genes. This demonstration of ''homologous'' genes for ''analogous'' processes and structures has wreaked havoc with our definitions of analogy and homology. The insect eye and the vertebrate eye are two examples of structures said to be analogous. However, they can be shown to both be based on the expression of the *Pax-6* gene (Quiring *et al.*, 1994), and it is probable that the vertebrate and insect (and cephalopod) eyes are the modified descendents of a basic metazoan photoreceptive cell that was regulated by Pax-6. It has recently been proposed (Chisholm and Horvitz, 1995) that the Pax-6 family initially functioned to pattern part of the head region (i.e., working as part of the anterior head field) and only subsequently evolved more specific sensory functions. Similarly, the *Xenopus* gene *chordin* and the *Drosophila* gene *short-gastrulation* have similar sequences and expression patterns, and they act similarly in vertebrate and insect gastrulation (to counter the lateralizing effects of BMP-4/decapentaplegic). Even though the types of gastrulation do not appear similar to any marked degree, the genes controlling them may be homologous (François and Bier, 1995; Holley *et al.*, 1995). Similarly, the heart of vertebrates and the heart of insects have hardly anything in common except their ability to pump fluids. Yet, they both appear to to be predicated upon the expression of the same gene, *Csx/tinman* (see Manak and Scott, 1994).

This gets us into an newly discovered and fascinating realm of homology—the homology of process (Gilbert, 1996b). Whereas classic homology has been one of structure—be it of skeletons or genes—the homology of process goes into the very mechanisms of development. Whereas classical homology looks at the similarities between entities, the homology of process concerns the similarities of dynamic interactions. The result is that although organs (such as the vertebrate and arthropod eye, the vertebrate and arthropod leg, etc.) can be structurally analogous, they may be formed by processes that are homologous!

One of the best examples of such a process is the receptor tyrosine kinase-ras signal transduction pathway that has recently been found in mice, nematodes, and fruit flies. In *Drosophila*, the determination of the photoreceptor seven is accomplished when the *sevenless* protein (on the presumptive photoreceptor 7) binds to the *bride of sevenless* protein (*boss*) on photoreceptor 8. This interaction activates the tyrosine kinase of the sevenless protein to phosphorylate itself. The *DRK* protein then binds to these newly phosphorylated tyrosines through its src-homology-2 (SH2) region and activates the *son of sevenless* (*SOS*) protein. This protein is a guanosine nucleotide exchanger and exchanges GDP for GTP on the Ras1 G protein. This activates the G protein, enabling it to transmit its signal to the nucleus through the MAP kinase cascade. This same system has been found to exist in the determination of the nematode vulva, the mammalian epidermis, and the *Drosophila* terminal segments. The similarity in these systems is so striking that many of the components are interchangeable between species. The gene for human GRB2 can correct the phenotypic defects of *sem-5*-deficient nematodes, and the nematode sem-5 protein can bind to the phosphorylated form of the human EGF receptor (see Greenwald and Rubin, 1992; Gilbert, 1994b). The process is thus historically (specifically) homologous between species (*Drosophila* retina/

nematode vulva) and serially homologous within species (*Drosophila* retina/*Drosophila* acron and telson).

Another important pathway involves the *Drosophila* wingless and hedgehog proteins. These proteins were found to be critical in the formation of segmental boundaries in the *Drosophila* embryo and of compartmental boundaries in the larval imaginal discs. During the formation of the parasegmental border of the embryo, the more posterior cell secretes the hedgehog protein. This protein binds to a receptor on the anterior cell and stimulates the production of the wingless protein. The wingless protein acts in a paracrine fashion to inhibit the zest-white 3 kinase in the neighboring cell. The inhibition of zw3 kinase releases the repression of the hedgehog gene, thus stabilizing the pathway. The wingless–hedgehog system is serially homologous in *Drosophila,* being used later in the eye, leg, and wing imaginal discs to specify the proximodistal axis (see Wilder and Perrimon, 1995). This system is also historically homologous. In vertebrates, there are several homologues to wingless, namely, the wnt proteins; the homologue to zest-white 3 is glycogen synthase kinase 3β (GSK-3β); and there are numerous *hedgehog* analogues, such as *sonic hedgehog.* In vertebrates, the wingless–hedgehog system is thought to be needed for producing the body axes (as in *Drosophila*) and the limbs (as in *Drosophila*). (Niswander *et al.,* 1994, Ingham, 1994; Laufer *et al.,* 1994.

So we not only have homologous genes, but homologous pathways in organisms as diverse as flies, frogs, and yeasts. We have come a long way from the time when Mayr (1966) could state concerning macroevolution: ''Much that has been learned about gene physiology makes it evident that the search for homologous genes is quite futile except in very close relatives.''

The Rediscovery of the Morphogenetic Field

When we look at the homology of process, we notice something else, as well. These interactions occur within particular collections of cells that had formerly been identified as being fields. These domains, the limb field, the eye field, the otic field, etc., were each isolatable, transplantable, and well-characterized landmarks on the embryo. In some areas of developmental biology, the concept of the field has persisted, and the notions of limb fields and heart fields are still in the literature (see Sater and Jacobson, 1990; Easton *et al.,* 1994; Cohn *et al.,* 1995). In such instances, no claims are usually made other than that these areas of mesoderm are destined to form these particular structures. In recent years, several developmental biologists have revitalized the ideas of fields and have reclaimed their fundamental importance for both development and evolution. Brian Goodwin (1982, 1995) has formulated a concept of a morphogenetic field whose nongenic mechanisms of action and wholism probably correspond quite well to the classical notions of Paul Weiss and Alexander Gurwitsch. However, this is a field that is outside developmental genetics and is actively opposed to gene action as being important in field functions. De Robertis and his associates (1991) synthesized molecular and classical material ''to increase awareness among modern developmental biologists of the old concepts of morphogenetic gradient fields.'' At that time, however, the interactions between parts of any field were still unknown, but De Robertis *et al.* (1991) emphasized the roles that homeobox genes may play in initiating and organizing these fields. Especially important to them were two observations concerning gradients produced by Hox proteins in limb buds. The first was that gradients of these proteins could induce the production of specific proteins at specific sites and that these proteins may establish the conditions for a field (such as the limb field or feather bud field) to emerge. The second notion was that the gradients of these proteins might establish the polar axes of these organs. Until recently, the interactions that constituted these fields could not be identified. However, the discovery of the homologous pathways of development has given us new insights into how these fields are established and maintained.

Molecular biologists have recently rediscovered fields in *Drosophila.* The imaginal discs of insects have long been considered as gradient fields (see French *et al.,* 1976; Ingham and Martinez Arias, 1992; Williams *et al.,* 1994), since they are well-defined groups of cells whose interactions form an organ, since they regulate to replace missing parts, and since they retain their ability to generate the particular organ when the disc is transplanted to other sites in the larva. The work from Cohen's and Carroll's laboratories is giving us a fascinating picture of how interactions within these fields create the leg is created and how changes in these interactions can cause altered morphologies (Diaz-Benjumea *et al.,* 1994; Williams *et al.,* 1994). The *Drosophila* leg field appears to be established by a rectilinear coordinate system whereby the Hom/Hox genes (*Scr, Antp, Ubx*) determine the anteroposterior zone of competence to form legs, whereas decapentaplegic expression is needed in the dorsoventral plane. The polarity of the leg is produced from the interaction of three compartments within the disc. The posterior compartment is defined by the synthesis of the engrailed protein and the secretion of hedgehog protein. The anterior dorsal compartment contains cells capable of producing decapentaplegic protein, and the anterior ventral compartment contains cells competent to express wingless. Upon induction by hedgehog protein, the band of dorsal cells immediately anterior to the posterior border synthesize decapentaplegic protein, while the ventral cells immediately adjacent to the posterior border produce the wingless protein. Those cells at the border of *decapentaplegic* and *wingless* expression regions are instructed to produce the distal-less protein, and these cells become the distalmost portion, the claw, of the leg. In this way, the anterior–posterior and dorsal–ventral compartments of the disc create the proximal–distal axis of the leg.

Few people would have expected that a similar situation would exist for another embryological field—the vertebrate limb field. After all, here is the classic example of analogy as opposed to homology. The insect and vertebrate legs

share the same function, but that's about it. The insect leg forms from the telescoping of the ectodermal imaginal disc. The vertebrate limb forms from the reciprocal induction of the Apical Ectodermal Ridge, the mesodermal Progress Zone mesenchyme, and the mesodermal Zone of Polarizing Activity. The insect leg has a cuticular exoskeleton, the vertebrate limb has a complex endoskeleton of cartilage and/or bone. There does not seem to be much in common. The vertebrate limb field is thought to be initiated by the localized secretion of fibroblast growth factor proteins (Cohn *et al.,* 1995). This, in turn, may be based on Hom/Hox genes such as *Hoxc-6* (which is present in the lateral plate mesoderm at the place where the forelimb bud will be formed; Oliver *et al.,* 1988; De Robertis *et al.,* 1991) or *Hoxb-8* (which is present in the posterior forelimb bud and whose duplication in the anterior of that bud leads to mirror-image duplications of the posterior forelimb; Charité *et al.,* 1994). Recently, several laboratories have shown that the same proteins that generate the insect leg also generate the vertebrate limbs. Just as hedgehog protein from the posterior portion of the insect leg disc activates the *decapentaplegic* gene, so sonic hedgehog protein from the ZPA mesoderm in the posterior of the bud activates BMP-2, a vertebrate analogue of decapentaplegic (Francis *et al.,* 1994). In addition, the expression of *sonic hedgehog* is activated by the diffusion of the wnt-7a protein (i.e., a wingless homolog) from the dorsal ectoderm (Yang and Niswander, 1995; Parr and McMahon, 1995). The molecular interactions within the field needed to create a zone of polarizing activity, to create an apical ectodermal ridge, and to create a progress zone mesoderm are now becoming known, and they resemble the interactions that create the axes of the insect limb. It seems that nature only figured how to make appendages once. Moreover, nature seems to like to use the same pathways over and over again in different fields to make different organs. The same decapentaplegic/hedgehog/wingless system appears to be working in the *Drosophila* eye-antennal disc, where the conjunction of ventral wingless, dorsal dpp, and posterior hh cause the synthesis of distal-less protein. It is assumed that the targets of these proteins are different in different discs, so that the genes for the appropriate organs are activated.

The concept of fields was also rediscovered by clinical geneticists. Given that a specific malformation (such as an extra thumb) can be caused by different mutations and be a component of different syndromes, it was established that the complex of anatomic structures that was malformed together constituted a dysmorphogenetically reactive unit. It was presumed that the same complex of anatomic structures constituted a morphogenetically reactive unit under *normal* circumstances. The *dysmorphogenetically* reactive fields defined on the basis of clinical syndromes were seen to be the equivalent of the self-organizing, spatially coordinated, and temporally synchronized *morphogenetic* fields of classical embryology. This equation was supplemented by the observations that in many vertebrate species, the same malformations (cyclopia, polydactyly, etc.) could be produced experimentally or by mutation (Opitz, 1985).

The above-mentioned fields are the so-called ''secondary'' fields. The ''primary field'' is the entire embryo during blastogenesis, before axis or cell determination. This is the field that guarantees that each egg produces one (and only one) embryo, despite the fact that many of the early blastomeres can produce an entire embryo if isolated from the others (Driesch, 1892; Hertwig, 1894; Spemann, 1919; Spratt and Haas, 1960). This primary morphogenetic field was ''rediscovered'' by several groups of embryologists, including developmental biologists who demonstrated that mutual inhibitory interactions were occurring between the embryonic cells (Henry *et al.,* 1989; Khaner and Eyal-Giladi, 1989; Khaner and Wilt, 1991), clinical geneticists who postulated such a field on the basis of clinical malformations (Opitz, 1993), and theorists (Raff *et al.,* 1991) who predicted such a global morphogenetic field on the evidence from development wherein evolutionary changes could occur only at particular times in the life cycle.

The molecular analysis of the primary morphogenetic field in *Xenopus* uncovered once again the activity of the *wnt* genes (McMahon and Moon, 1989; Pierce and Kimelman, 1995; He *et al.,* 1995). According to the wnt signaling pathway, wnt acts to suppress activity or synthesis of the zw3/GSK-3β gene product. If the pathway were blocked such that GSK-3β is insensitive to inhibition by wnt, no primary axis is formed. Even more interestingly, when GSK3β is completely removed (by molecular means), two, three, and even four dorsal axes form in the frog embryo. One can also obtain frogs with multiple axes by adding excess wnt mRNA. It appears, then, that the wnt pathway is critical for maintaining embryonic individuality.

SUMMARY

We can now integrate these ideas together into the beginnings of a theory that includes homology, macroevolution, and the developmental genetics of morphogenetic fields. Morphogenetic fields assume the primary organizing activity here, as well as in the embryo.

1. Fields are discrete units of embryonic development. They are produced by the interactions of genes and gene products within specific bounded domains. They are therefore defined in terms of information that becomes translated into spatial entities. Fields can be limited by diffusion, competence, gap junctions, or cell adhesion molecules. Changes in these properties of the field result in changes in phenotype and lead to evolutionary novelty. Other changes *within* the fields (such as those involving changes in the amount, type, or duration of gene products or those involving mutations that alter the specificity DNA-protein binding) can also cause evolutionary alterations.

2. Morphogenetic fields are modular entities. This modularity is an important key to biological order. The informa-

tion content or determinacy of a complex anatomical structure is orders of magnitude higher than that of the genome, and such order rises from the use of standard parts, which are arranged hierarchically, and which can interact with each other (Riedl, 1977). Embryonic modules such as morphogenetic fields and organ rudiments are genetically specified, have autonomous attributes and hierarchical organization, and can change with regard to location, time, and interactions with other modules (Raff, 1996). Thus, a dynamic modular structure is characteristic of metazoan organisms and is a property of fields as well.

3. Although located in the same places, these rediscovered morphogenetic fields are not the same fields as those postulated by Gurwitsch, Spemann, or Weiss. The older morphogenetic fields were anatomically and cytoplasmically defined entities that were innocent of genes. The new conceptions of morphogenetic fields are based on genetically defined interactions among cells, and the limits of competence can be established by homeotic genes. The ''high-in-the-herarchy'' genes, such as those encoding transcription factors Pax-6 and Lim1, most likely act to establish such fields.

4. Homologous morphogenetic fields can exist within the same organism (serial process homology) or between different organisms (orthologous process homology). An example of serial process homology include the ras pathway in the retinal fields and the terminal segment fields of *Drosophila.* This pathway is orthogonally homologous to the epidermal differentiation pathway in mammals. The expression of the Hom/Hox genes across the anterior–posterior axis of vertebrate and insect embryos would also constitute an orthologous homologous field between species, and the use of the same genes in mice or chicks to generate the dorsoventral axis of the limb would constitute a serially homologous field in those organisms. Evolution depends on the replication and modification of morphogenetic fields. This may be seen in the origins of novel structures (insect jaws, turtle carapace, butterfly wing eyespots) using the existing limb fields (Burke, 1989; Panganiban *et al.,* 1994; Carroll *et al.,* 1994). The mechanisms by which fields can be replicated and then altered is a new area of research which should produce new insights into the mechanisms of evolution (Jernvall, in press; Nijhout and Paulsen, personal communication).

5. Homologous genes/proteins can play different roles in different fields. For example, sonic hedgehog activates different proteins in different fields. It works as a ZPA morphogen within the limb field and as the inducer of floorplate and motor neuron differentiation in the neuraxis field. Similarly, the rel protein pathway is used in insects to establish the ventral mesodermal cells (through the separation of the dorsal protein from the cactus protein), while vertebrates use a homologous pathway of homologous genes for activating immunoglobulin production (through the separation of NF-κB from IκB) (Kidd, 1992; Shelton and Wasserman, 1993).

6. The fields explain pleiotropic and polytopic syndromes. In syndromes wherein a single mutant gene (or gene pair) produces multiple congenital anomalies, several organs may be affected together. In polytopy (Opitz, 1993), organs are affected that are linked together in some intercellular developmental pathway. Here, for example, we see that the renal-limb deficiencies might be explained because early in development, they belong to a common field (Dieker and Opitz, 1969). Paracrine factors from the mesonephros (probably insulin-like growth factor I) are needed to promote the initial growth of the limb bud (Geduspan and Solursh, 1992, 1993). Similarly, renal and gonadal tissues are often affected together, since these organs constitute a common field early in development. The syndromes such as DiGeorge syndrome, CATCH-22 syndrome, and MEN-2A, each have their disparate symptoms joined by a defect in the neural crest fields of the mammalian embryo (see Scambler, 1994). We also know that different mutations can create the same phenotype by affecting the same field. Thus, overexpression of *wnt* and deletions of *zeste--white 3* give the same or related phenotype. Multiple malformations occuring in syndromes can also be caused by true (''mosaic'') pleiotropy (Hadorn, 1961; Grüneberg, 1962) wherein the organs cannot be joined together in a common field. In these cases, the same molecule is thought to be used in several different fields. Since *msx-2* genes are expressed in developing limbs and teeth, we would expect a deficiency in *msx-2* to result in deformities of these two structures, even though there is no connection between these two organs as they develop. Indeed, the deficiency of *msx-2* in humans leads to a condition characterized by such abnormalities (Jabs *et al.,* 1993).

7. The field acts like ''an ecosystem'' (Weiss), and the deletions of certain genes can be regulated for under certain conditions. For example, the deletion of myoD in muscle cells does not lead to marked deficiencies since within the field, it represses a similar gene, myf-5. When MyoD is absent, myf-5 is no longer repressed and can function like MyoD (Rudnicki *et al.,* 1993). This accounts for the ''buffering'' noted by Waddington and the redundancy (''belt and suspenders'') noted by Spemann. The morphogenetic field thus unites the atomism of the genetic and biochemical pathways within the wholism of the developmental pathway.

8. The gene effects morphogenesis by operating within the field; it has to work in concert with other genes in order to function. It has long been known that the same gene inherited through different generations can become expressed severely or benignly depending on its ''background.'' Freire-Maia (1975), for example, reports that within one family, a mutant gene caused limb abnormalities ranging from severe phocomelia to a mild abnormality of the thumb. This can be also be seen in malformations of gonad formation. The Y-linked SRY gene needed for testis morphogenesis of one particular strain of *Mus musculus* cannot function to produce testes when placed into a different strain of the same species (Eicher and Washburn, 1983). Similarly, the SRY gene of the AKR strain of mouse is not able to produce a testis when placed into a C57 strain. Another gene, on chromosome 17 of the C57 strain, cannot

cooperate with the AKR Y chromosome (Eicher and Washburn, 1989). Thus, while each gene is perfectly wild-type within its own strain, it acts a a deficient mutant when placed in a different background.

9. Cooperation between inducer and responder cell types is critical, and changes in these inducers or responders can alter development. This can happen in several ways. First, there can be a ''transfer of competence.'' If a pathway is established such that a receptor binds a ligand and initiates the cascade once the ligand is bound, then the pathway can be activated by a different molecule if the receptor changes. This can be accomplished experimentally, and it can explain phenomena such as Waddington's ''genetic assimilation,'' I. I. Schmalhausen's ''stabilizing selection,'' and G. G. Simpson's ''Baldwin effect.'' There are several candidates for this occurring during evolution (see Gilbert, 1994b; Sommer and Sternberg, 1994). Second, if the receptor or if the inducer changes its level or duration of activity, it can alter the morphology of the organ. For instance, if the receptors for a growth factor stayed active for one more cell division, or if the cells secreting the growth factor produced these factors for longer periods of time while the responding cells remained competent, then the organ would be greatly enlarged. It is possible that heterochronies and allometries can be produced in this fashion. Third, the requirement for cells to interact within a field could be a mechanism for speciation. The evolution of receptor–ligand systems such as those studied for bindin (Hofmann and Glabe, 1994) and growth hormones (Moyle *et al.*, 1994) may be crucial for discussions of how species diverge from common ancestors.

10. Just as the cell is seen to be the unit of structure and function in the body—not the genes that act through it—so the morphogenetic field can be seen as a major unit of ontogenetic and phylogenetic change. In declaring the morphogenetic field to be a major module of developmental and evolutionary change, we are, of course, setting it up as an alternative to the solely genetic model of evolution and development. This, however, is not to be seen as antagonistic to the principle that genes are important in evolution or development. This is not in any way denied. But just as the genes make the cells and the cells form the body, so the gene products first need to interact to create morphogenetic fields in order to have their effects. Changes in these fields then change the ways that animals develop.

CODA

In 1895, Wilhelm Roux, in his manifesto for experimental embryology, postulated that there would be two types of developmental mechanics. The first—*ontogenetic* developmental mechanics—would uncover how development occurred. The second—*phylogenetic* developmental mechanics—would determine how changes in embryonic development caused evolutionary change. A century later, we are starting to make good on Roux's prophecy. The homologies of process within morphogenetic fields provide some of the best evidence for evolution—just as skeletal and organ homologies did earlier. Thus, the evidence for evolution is better than ever. The role of natural selection in evolution, however, is seen to play less an important role. It is merely a filter for unsuccessful morphologies generated by development. Population genetics is destined to change if it is not to become as irrelevant to evolution as Newtonian mechanics is to contemporary physics. The population genetics of regulatory genes and their possible combinations within fields should become a major new research program. Developmental genetics would also change, reflecting an emphasis on the initiation and maintainance of genetic circuits within cells and epigenetic circuits within the field. One of its major research programs would be to find the target genes of these pathways which differ from field to field and from organism to organism, i.e., those genes that provide the diversity in evolution.

Developmental biology is reclaiming its appropriate place in evolutionary theory. We conclude with a remarkable prophecy from one of those evolutionary-minded embryologists, Gavin de Beer (1951), who saw homology and fields as being crucial to the study of evolution:

> But since phylogeny is but the result of modified ontogeny, there is the possibility of a causal analytic study of present evolution in an experimental study of the variability and genetics of ontogenetic processes. Finally, it may be possible that, freed from the trammels and fetters which have so long confined thought, the whole of the animal kingdom may appear in a new light, more homogeneous and compact than had been imagined, and with the gaps between its major groups less formidable and perhaps even bridgeable.

ACKNOWLEDGMENTS

The authors acknowledge the constructive criticisms of Drs. I. Dawid, E. M. De Robertis, and J. Jernvall on earlier drafts of the manuscript.

REFERENCES

Adams, M. B. (1990). La génétique des populations: Etait-elle une génétique evolutive? *In* ''Histoire de la Génétique: Pratiques, Techniques et Théories'' (J.-L. Fischer and W. H. Schneider, Eds.), pp. 152–171. Editions Sciences, Paris.

Alberch, P. (1982). Developmental constraints in evolutionary processes. *In* ''Evolution and Development: Report of the Dahlem Workshop on Evolution and Development'' (J. T. Bonner, Ed.), pp. 313–332. Springer-Verlag, New York.

Allen, G. E. (1978). ''Life Science in the Twentieth Century.'' Cambridge Univ. Press, NY.

Ayala, F. J. (1983). Microevolution and macroevolution. *In* ''Evolution from Molecules to Men'' (D. S. Bendall, Ed.), pp. 387–402. Cambridge Univ. Press, Cambridge.

Bachiller, D., Macias, D., Duboule, D., and Morata, G. (1994). Con-

servation of a functional hierarchy between mammalian and insect Hox/HOM genes. *EMBO J.* 13, 1930–1941.
Baldwin, J. M. (1902). ''Development and Evolution.'' Macmillan Co., New York.
Bateson, W. (1894). ''Materials for the Study of Variation, Treated with Especial Regard to Discontinuity in the Origin of Species.'' Macmillan Co., New York.
Beadle, G., and Ephrussi, B. (1937). Development of eye colors in *Drosophila:* Diffusible substances and their interrelations. *Genetics* 22, 76–86.
Beatty, J. (1994). Opportunities for genetics in the atomic age. Paper presented at the Mellon Symposium, ''Institutional and Disciplinary Contexts of the Life Sciences,'' Massachusetts Inst. Technol., Cambridge, MA.
de Beer, G. R. (1940). ''Embryos and Ancestors.'' Oxford Univ. Press, Oxford.
de Beer, G. R. (1951). ''Embryos and Ancestors,'' revised ed. Oxford Univ. Press, Oxford.
Berrill, N. J. (1941). Spatial and temporal growth patterns in colonial organisms. *Growth (Suppl.)* 5, 89–111.
Boveri, T. (1910). Die Potenzen der Ascaris-Blastomeren bei abgeänderter Furchung, zugleich ein Beitrag zur Frage qualitativ-ungleicher Chromosomen-Teilung. *In* ''Festschrift für Richard Hertwig, Vol. 3.'' Fischer, Jena.
Britten, R. J. (1967). *Carnegie Inst. Wash. Yearbook* 66, 68.
Britten, R. J., and Kohne, D. (1968). Repeated sequences in DNA. *Science* 161, 529–540.
Burke, A. C. (1989). Development of the turtle carapace: Implications for the evolution of a novel bauplan. *J. Morphol.* 199, 363–378.
Burke, A. C., Nelson, A. C., Morgan, B. A., and Tabin, C. (1995). Hox genes and the evolution of vertebrate axial morphology. *Development* 121, 333–346.
Carraco, A. E., McGinnis, W., Gehring, W. J., and De Robertis, E. M. (1984). Cloning of an *X. laevis* gene expressed during embryogenesis coding for a peptide region homologous to *Drosophila* homeotic genes. *Cell* 37, 409–414.
Carroll, S. B., Gates, J., Keys, D. N., Paddock, S. W., Panganiban, G. E. F., Selegue, J. E., and Williams, J. A. (1994). Pattern formation and eyespot determination in butterfly wings. *Science* 265, 109–114.
Charité, J., DeGraaff, W., Shen, S. B., and Deschamps, J. (1994). Ectopic expression of *Hoxb*-8 causes duplications of the ZPA in the forelimb and homeotic transformation of axial structures. *Cell* 78, 589–601.
Child, C. M. (1915). ''Individuality in Organisms.'' Univ. of Chicago Press, Chicago.
Child, C. M. (1941). ''Patterns and Problems of Development.'' Univ. of Chicago Press, Chicago.
Chisaka, O., and Cappecchi, M. R. (1991). Regionally restricted developmental defects resulting from targeted disruption of the homeobox gene *hox 1.5. Nature* 350, 473–479.
Chisholm, A. D., and Horvitz, H. R. (1995). Patterning of the *Caenorhabditis elegans* head region by the *Pax-6* family member *vab-3. Nature* 377, 52–55.
Cohn, M. J., Izpisúa-Belmonte, J. C., Abud, H., Heath, J. K., and Tickle, C. (1995). Fibroblast growth factors induce additional limb development from the flank of chick embryos. *Cell* 80, 739–746.
De Robertis, E. A., Morita, E. M., and Cho, K. W. Y. (1991). Gradient fields and homeobox genes. *Development* 112, 669–678.
Diaz-Benjumea, F. J., Cohen, B., and Cohen, S. M. (1994). Cell interaction between compartments establishes the proximal-distal axis of *Drosophila* legs. *Nature* 372, 175–179.
Dieker, H., and Opitz, J. M. (1969). Associated acral and renal malformations. *Birth Defects Orig. Artic. Ser.* 5(3), 68–77.
Dobzhansky, T. (1937). ''Genetics and the Origin of Species.'' Columbia Univ. Press, New York.
Dobzhansky, T. (1951). ''Genetics and the Origin of Species.'' 3rd ed. Columbia Univ. Press, New York.
Driesch, H. (1892). The potency of the first two cleavage cells in echinoderm development. Experimental production of partial and double formations. *In* ''Foundations of Experimental Embryology'' (B. H. Willier and J. M. Oppenheimer, Eds.), pp. 38–50. Hafner, New York.
Easton, H. S., Armstrong, J. B., and Smith, S. C. (1994). Heart specification in the Mexican axolotl. *Dev. Dyn.* 200, 313–320.
Edelman, G. (1988). ''Topobiology.'' Basic Books, New York.
Eicher, E. M., and Washburn, L. (1983). Inherited sex reversal in mice: Identification of a new primary sex-determining gene. *J. Exp. Zool.* 228, 297–304.
Eicher, E. M., and Washburn, L. (1989). Normal testis determination in the mouse depends on genetic interaction of a locus on chromosome 17 and the Y chromosome. *Genetics* 123, 173–179.
Eldredge, N., and Gould, S. J. (1972). Punctuated equilibria: An alternative to phyletic gradualism. *In* ''Models of Paleobiology'' (T. J. M. Schopf, Ed.), pp. 82–115.
Filipchenko, I. A. (1929). ''Izmenchivost' i Metody ee Izucheniia,'' 4th ed. Gosidzat, Leningrad.
Fitch, W. M. (1970). Distinguishing homologous from analogous proteins. *Syst. Zool.* 19, 99–113.
Francis, P. H., Richardson, M. K., Brickell, P. M., and Tickle, C. (1994). Bone morphogenesis proteins and a signal transduction pathway that controlls patterning in the developing chick limb. *Development* 120, 209–218.
François, V., and Bier, E. (1995). *Xenopus chordin* and *Drosophila short gastrulation* genes encode homologous proteins functioning in dorsal-ventral axis formation. *Cell* 80, 19–20.
French, V., Bryant, P. J., and Bryant, S. V. (1976). Pattern regulation in epimorphic fields. *Science* 193, 969–981.
Freire-Maia, N. (1975). A heterozygote expression of a ''recessive'' gene. *Hum. Hered.* 25, 302–304.
Gasman, D. (1971). ''The Scientific Origins of National Socialism.'' MacDonald, London.
Gaunt, S. J. (1994). Conservation in the Hox code during morphological evolution. *Int. J. Dev. Biol.* 38, 549–552.
Geduspan, J. S., and Solursh, M. (1992). A growth-promoting influence from the mesonephros during limb outgrowth. *Dev. Biol.* 151, 242–250.
Geduspan, J. S., and Solursh, M. (1993). Effects of the mesonephros and insulin-like growth factor I on chondrogenesis of limb explants. *Dev. Biol.* 156, 177–187.
Geoffroy-Saint-Hilaire, É. (1830). ''Principes de Philosophie Zoologique, discutés en Mars, 1830, au Sein de l'Académie Royale des Sciences.'' Pichon et Didier, Paris.
Gilbert, S. F. (1978). The embryological origins of the gene theory. *J. Hist. Biol.* 11, 307–351.
Gilbert, S. F. (1980). Owen's vertebral archetype and evolutionary genetics: A Platonic appreciation. *Perspect. Biol. Med.* 23, 475–488.
Gilbert, S. F. (1988). Cellular politics: Just, Goldschmidt, and the attempts to reconcile embryology and genetics. *In* ''The American Development of Biology'' (R. Rainger, K. Benson, J. Maiensch-

ein, Eds.), pp. 311–346. Univ. of Pennsylvania Press, Philadelphia.
Gilbert, S. F. (1994a). Dobzhansky, Waddington, and Schmalhausen: Embryology and the Modern Synthesis. *In* ''The Evolution of Theodosius Dobzhansky'' (M. Adams, Ed.), pp. 143–154. Princeton Univ. Press, Princeton.
Gilbert, S. F. (1994b). ''Developmental Biology.'' 4th ed. Sinauer, Sunderland, MA.
Gilbert, S. F. (1996a). Adaptive enzymes and the entrance of molecular biology into embryology. *In* ''The History of Molecular Biology'' (S. Sarkar, Ed.), Kluwer Academic, Dordrecht, in press.
Gilbert, S. F. (1996b). Cellular dialogues during development. *In* ''Gene Regulation and Fetal Development: Procedings of the Third International Congress on Fetal Genetic Pathology'' (G. Neri, E. Martini-Neri, and J. M. Opitz, Eds.). Wiley–Liss, New York, in press.
Gilbert, S. F., and M. Faber. (1996). Looking at embryos: The visual and conceptual aesthetics of emerging form. *In* ''Aesthetics and Science: The Elusive Synthesis'' (A. I. Tauber, Ed.). Kluwer Academic, Dordecht, in press.
Gluecksohn-Schoenheimer, S. (1938). The development of two tailless mutants in the house mouse. *Genetics* 23, 573–584.
Goldschmidt, R. B. (1940). ''The Material Basis of Evolution.'' Yale Univ. Press, New Haven.
Goodwin, B. (1982). Development and evolution. *J. Theoret. Biol.* 97, 43–55.
Goodwin, B. (1995). ''How the Leopard Changed its Spots: The Evolution of Complexity.'' Scribner's, New York.
Gottlieb, G. (1992). ''Individual Development and Evolution: The Genesis of Novel Behavior.'' Oxford Univ. Press, New York.
Gould, S. J. (1977). ''Ontology and Phylogeny.'' Harvard Univ. Press, Cambridge.
Gould, S. J. (1980). Is a new general theory of evolution emerging? *Paleobiology* 6, 119–130.
Gould, S. J. (1982). The meaning of punctuated equilibrium and its role in validating a hierarchical approach to macroevolution. *In* ''Perspectives in Evolution'' (R. Milkman, Ed.), pp. 83–104. Sinauer, Sunderland, MA.
Gould, S. J., and Lewontin, R. C. (1979). The spandrels of San Marco and the Panglossian paradigm: A critique of the adaptationist program. *Proc. R. Soc. London Ser. B* 205, 581–598.
Gregory, W. K. (1917). Genetics versus paleontology. *Am. Nat.* 51, 622–635.
Greenwald, I., and Rubin, G. M. (1992). Making a difference: The role of cell–cell interactions in establishing separate identities for equivalent cells. *Cell* 68, 271–281.
Grüneberg, H. (1962). ''The Pathology of Development.'' Blackwell, Oxford.
Gurwitsch, V. A. (1910). Über Determination, Normierung und Zufall in der Ontogenese. *Arch. Entwicklungsmech. Org.* 30, 133–193.
Gurwitsch, V. A. (1912). Die Vererbung als Verwirklichungsvorgang. *Biol. Centralblatt.* 32, 458–486.
Gurwitsch, V. A. (1922). Über den Begriff des embryonalen Feldes. *Roux's Arch. Entwicklungsmech. Org.* 51, 383–415.
Hadorn, E. (1961). ''Developmental Genetics and Lethal Factors'' (U. Mittwoch, trans.). Wiley, New York.
Hall, B. K. (Ed.) (1994). ''Homology: The Hierarchical Basis of Comparative Anatomy.'' Academic Press, New York.
Hamburger, V. (1980). Embryology and the Modern Synthesis in evolutionary theory. *In* ''The Evolutionary Synthesis: Perspectives on the Unification of Biology'' (E. Mayr and W. Provine, Eds.), pp. 97–112. Cambridge Univ. Press, NY.
Haraway, D. J. (1976). ''Crystals, Fabrics, and Fields: Metaphors of Organicism in Twentieth-Century Developmental Biology.'' Yale Univ. Press, New Haven.
Harrison, R. G. (1918). Experiments on the development of the forelimb of *Amblystoma*, a self-differentiating equipotential system. *J. Exp. Zool.* 25, 413–461.
Harrison, R. G. (1937). Embryology and its relations. *Science* 85, 369–374.
Harwood, A. J., Plyte, S. E., Woodgett, J., Strutt, H., and Kay, R. R. (1995). Glycogen synthase kinase 3 regulates cell fate in *Dictyostelium*. *Cell* 80, 139–148.
He, X., Saint-Jeannet, J.-P., Woodgett, J. R., Varmus, H. E., and Dawid, I. B. (1995). Glycogen synthase kinase 3 and dorsoventral patterning in *Xenopus* embryos. *Nature* 374, 617–622.
Henry, J., Amemiya, S., Wray, G. A., and Raff, R. (1989). Early inductive interactions are involved in restricting cell fates of the mesomeres in sea urchin embryos. *Dev. Biol.* 136, 140–153.
Herrmann, H. (1964). Biological field phenomena: Facts and concepts. *In* ''Form and Strategy in Science'' (J. R. Gregg and F. T. C. Harris, Eds.), pp. 343–362. Reidel, Dordrecht.
Hertwig, O. (1894). ''The Biological Probem of Today: Preformation or Epigenesis?'' (P. C. Mitchell, trans.). Macmillan Co., New York.
Hofmann, A., and Glabe, C. (1994). Bindin, a multifunctional sperm ligand and the evolution of new species. *Semin. Dev. Biol.* 5, 233–242.
Holley, S. A., Jackson, P. D., Sasai, Y., Lu, B., De Robertis, E. M., Hoffmann, F. M., and Ferguson, E. L. (1995). A conserved system for dorsal-ventral patterning in insects and vertebrates involving *short gastrulation* and *chordin*. *Nature* 376, 249–253.
Huxley, J. (1932). ''Problems of Relative Growth.'' Dial Press, New York.
Huxley, J., and de Beer, G. R. (1934). ''The Elements of Experimental Embryology.'' Cambridge Univ. Press, Cambridge.
Huxley, T. H. (1858). On the theory of the vertebrate skull. *Sci. Memoirs* 1, 538–606.
Ingham, P. W. (1994). Hedgehog points the way. *Curr. Biol.* 4, 1–4.
Ingham, P. W., and Martinez Arias, A. (1992). Boundaries and fields in early embryos. *Cell* 68, 221–235.
Jabs, E. W., and 11 others. (1993). A mutation in the homeodomain of the human *MSX2* gene in a family affected with autosomal dominant craniosynostosis. *Cell* 75, 443–450.
Jernvall, J. (1995). Mammalian molar cusp patterns: developmental mechanisms of diversity. Thesis. *Acta Zool. Fennica* 198, 1–61.
Jukes, T. (1968). ''Molecules and Evolution.'' Columbia Univ. Press, New York.
Kettlewell, H. B. D. (1959). Darwin's missing evidence. *Sci. Am.* 200(3), 48–53.
Khaner, O., and Eyal-Giladi, H. (1989). The chick's marginal zone and primitive streak formation. I. Coordinative effect of induction and inhibition. *Dev. Biol.* 134, 206–214.
Khaner, O., and Wilt, F. (1991). Interactions of different vegetal cells with mesomeres during early stages of sea urchin development. *Development* 112, 881–890.
Kidd, S. (1992). Characterization of the *Drosophila cactus* locus and analysis of interactions between cactus and dorsal proteins. *Cell* 71, 623–635.
King, M.-C., and Wilson, A. C. (1975). Evolution at two levels in humans and chimpanzees. *Science* 188, 107–116.

Krumlauf, R. (1993). *Hox* genes and pattern formation in the branchial region of the vertebrate head. *Trends Genet.* 9, 106–112.

Lammer, E. J., and Opitz, J. M. (1986). The DiGeorge anomaly as a developmental field effect. *Am. J. Med. Genet.* 2, 143–150.

Laufer, E., Nelson, C. E., Johnson, R., Morgan, B. A., and Tabin, C. (1994). Sonic hedgehog and Fgf-4 act through a signalling cascade and feedback loop to integrate growth and patterning of the developing limb bud. *Cell* 79, 993–1003.

Lewis, E. B. (1978). A gene complex controlling segmentation in *Drosophila. Nature* 276, 565–570.

Lewis, E. B. (1985). Regulation of the genes of the bithorax complex in *Drosophila. Cold Spring Harbor Symp. Quant. Biol.* 50, 155–164.

Lillie, F.R. (1898). Adaptation in cleavage. *In* ''Biological Lectures from the Marine Biological Laboratories, Woods Hole, Massachusetts.'' pp. 43–67. Ginn, Boston.

Maienschein, J. (1991). ''Transforming Traditions in American Biology, 1880–1915.'' Johns Hopkins Univ. Press, Baltimore.

Malicki, J., Cianetti, L. C., Peschle, C., and McGinnis, W. (1992). Human HOX4B regulatory element provides head-specific expression in *Drosophila* embryos. *Nature* 358, 345–347.

Manak, J. R., and Scott, M. P. (1994). A class act: Conservation of homeodomain protein functions. *Development Suppl.* 61–71.

Mayr, E. (1966). ''Animal Species and Evolution.'' Harvard Univ. Press, Cambridge.

McGinnis, N., Kuziora, M. A., and McGinnis, W. (1990). Human *Hox 4.2* and *Drosophila Deformed* encode similar regulatory specificities in *Drosophila* embryos and larvae. *Cell* 63, 969–976.

McGinnis, W., and Krumlauf,R. (1992). Homeobox genes and axial patterning. *Cell* 68, 283–302.

McMahon, A. P., and Moon, R. T. (1989). Ectopic expression of the proto-oncogene int-1 in *Xenopus* embryos leads to duplication of the embryonic axis. *Cell* 58, 1075–1084.

Mitman, G., and Fausto-Sterling, A. (1992). Whatever happened to Planaria? C. M. Child and the physiology of inheritance. *In* ''The Right Tool for the Right Job: At Work in Twentieth-Century Life Sciences,'' (A. E. Clarke and J. H. Fujimura, Eds.), pp. 172–197. Princeton Univ. Press, Princeton.

Monod, J. (1971). ''Chance and Necessity.'' Knopf, New York.

Morgan, T. H. (1926a). ''The Theory of the Gene.'' Yale Univ. Press, New York.

Morgan, T. H. (1926b). The genetics and physiology of development. *Am. Nat.* 60, 489–515.

Morgan, T. H. (1932a). The rise of genetics. *Science* 76, 261–288.

Morgan, T. H. (1932b). ''The Scientific Basis of Evolution.'' Norton, New York.

Morgan, T. H. (1934). ''Embryology and Genetics.'' Columbia Univ. Press. New York.

Moyle, W. R., Campbell, R. K., Myers, R. V., Bernard, M. P., Han, Y., and Wang, X. (1994). Co-evolution of ligand-receptor pairs. *Nature* 368, 251–255.

Needham, J. (1931). ''Chemical Embryology.'' Cambridge Univ. Press, Cambridge.

Needham, J. (1950). ''Biochemistry and Morphogenesis.'' Cambridge Univ. Press, Cambridge.

Niswander, L., Jeffrey, S., Martin, G. R., and Tickle, C. (1992). A positive feedback loop coordinates growth and patterning in the vertebrate limb. *Nature* 371, 609–612.

Oliver, G., Wright, C. V. E., Hardwicke, J., and De Robertis, E. M. (1988). A gradient of homeodomain protein in developing forelimbs of *Xenopus* and mouse embryos. *Cell* 55, 1017–1024.

Ohno, S. (1960). ''Evolution by Gene Duplication.'' Springer-Verlag, New York.

Opitz, J. M. (1985). The developmental field concept. *Am. J. Med. Genet.* 21, 1–11.

Opitz, J. M. (1993). Blastogenesis and the primary field in human development. *Birth Defects Orig. Artic. Ser.* 29, 1–34.

Oppenheimer, J. M. (1966). The growth and development of developmental biology. *In* ''Major Problems in Developmental Biology'' (M. Locke, Ed.), pp. 1–27. Academic Press, New York.

Osborn, H. F. (1925). The origin of species as revealed by vertebrate paleontology. *Nature* 115, 961–963.

Owen, R. (1848). ''On the Archetype and Homologies of the Vertebrate Skeleton.'' Taylor, London.

Panganiban, G. E. F., Nagy, L., and Carroll, S. B. (1994). The role of the *distal-less* gene in the development and evolution of insect limbs. *Curr. Biol.* 4, 671–675.

Parr, B. A., and McMahon, A. P. (1995). Dorsalizing signal Wnt-7a required for normal polarity of D-V and A-P axes of mouse limb. *Nature* 374, 350–353.

Paul, D. B. (1988). The selection of ''survival of the fittest.'' *J. Hist. Biol.* 21, 411–424.

Pierce, S. B., and Kimelman, D. (1995). Regulation of Spemann organizer formation by the intracellular kinase Xgsk-3. *Development* 121, 755–765.

Quiring, R., Walldorf, U., Kloter, U., and Gehring, W. J. (1994). Homology of the *eyeless* gene of *Drosophila* to the *Small eye* gene in mice and *Aniridia* in humans. *Science* 265, 785–789.

Raff, R. A. (1996). ''The Shape of Life. Genes, Development, and the Evolution of Animal Form.'' Univ. of Chicago Press, Chicago, in press.

Raff, R. A., and Kaufman, T. C. (1983). ''Embryos, Genes, and Evolution.'' Macmillan Co., New York.

Raff, R. A., Wray, G. A., and Henry. J. J. (1991). Implications of radical evolutionary changes in early development for concepts of developmental constraint. *In* ''New Perspectives in Evolution'' (L. Warren and M. Meselson, Eds.), pp. 189–207. Wiley–Liss, New York.

Reidl, R. (1978). ''Order in Living Organisms: A Systems Analysis of Evolution'' (R. P. S. Jefferies, trans.). Wiley, New York.

Riddihough, G. (1992). Homing in on the homeobox. *Nature* 357, 643–644.

Rijli, F. M., Mark, M., Lakkaraju, S., Dierlich, A., Dollé, P., and Chambon, P. (1993). A homeotic transformation is generated in the rostral branchial region of the head by the disruption of *Hoxa-2,* which acts as a selector gene. *Cell* 75, 1333–1349.

Roth, V. L. (1984). On homology. *Biol. J. Linn. Soc.* 22, 13–29.

Roux, W. (1895). Einleitung. *Roux's Arch. Entwicklungsmech. Org.* 1, 1–42. Translated (W. M. Wheeler) as The problems, methods, and scope of developmental mechanics. Reprinted in Maienschein, J. (1986) ''Defining Biology,'' pp. 107–148. Harvard Univ. Press, Cambridge.

Rudnicki, M. A., Schnegelsberg, P. N. J., Stead, R. H., Braun, T., Arnold, H.-H., and Jaenisch, R. (1993). MyoD or myf-5 is required in a functionally redundant manner for the formation of skeletal muscle. *Cell* 75, 1351–1359.

Sander, K. (1994). Of gradients and genes: Developmental concepts of Theodor Boveri and his students. *Roux's Arch. Dev. Biol.* 203, 295–297.

Sater, A. K., and Jacobson, A. G. (1994). Restriction of the heart morphogenetic field in *Xenopus laevis. Dev. Biol.* 140, 328–336.

Scambler, P. J. (1994). DiGeorge Syndrome and related birth defects. *Semin. Dev. Biol.* 5, 303–310.

Schultz, J. (1935). Aspects of the relation between genes and development in *Drosophila*. *Am. Nat.* 69, 30–54.

Shelton, C. A., and Wasserman, S. A. (1993). *pelle* encodes a protein kinase required to establish dorsal-ventral polarity in the *Drosophila* embryo. *Cell* 72, 515–525.

Slack, J. M. W., and Tannahill, D. (1992). Mechanism of anterioposterior specification in vertebrates: Lessons from amphibians. *Development* 114, 285–302.

Slack, J. M. W., Holland, P. W. H., and Graham, C. F. (1993). The zootype and the phylotypic stage. *Nature* 361, 490–492.

Smocovitis, V. B. (1994). Organizing evolution: founding the society for the study of evolution (1939–1950). *J. Hist. Biol.* 27, 241–310.

Sommer, R. J., and Sternberg, P. W. (1994). Changes of induction and competence during the evolution of vulva development in nematodes. *Science* 265, 114–118.

Spemann, H. (1919). Experimentelle Forschungen zum Determinations- und Individualitäts-problem. *Naturwiss.* 7, 581–591.

Spemann, H. (1921). Die Erzeugung tierischer Chimaeren durch heteroplastiche embryonale Transplantation zwischen Triton cristatus u. taeniatus. *Roux's Arch. Entwicklungsmech. Org.* 48, 533–570.

Spemann, H. (1938). ''Embryonic Development and Induction.'' Yale Univ. Press, New Haven.

Spiegelman, S. (1948). Differentiation as the controlled production of unique enzymatic patterns. *In* ''Growth in Relation to Differentiation and Morphogenesis'' (J. F. Danielli, and R. Brown, Eds.), pp. 286–325. Cambridge Univ. Press, Cambridge.

Spratt, N. T., Jr., and Haas, H. (1960). Integrative mechanisms in the development of early chick blastoderm. I. Regulated potentiality of separate parts. *J. Exp. Zool.* 145, 97–138.

Stanley, S. M. (1979). ''Macroevolution: Pattern and Process.'' Freeman, San Francisco.

Swett, F. A. (1923). The prospective significance of the cells contained in the four quadrants of the primitive limb disc of *Amblystoma*. *J. Exp. Zool.* 37, 207–217.

Van Valen, L. (1982). Homology and causes. *J. Morphol.* 173, 305–312.

Waddington, C. H. (1940). ''Organisers and Genes.'' Cambridge Univ. Press, Cambridge.

Waddington, C. H. (1966). Fields and gradients. *In* ''Major Problems in Developmental Biology'' (M. Locke, Ed.), pp. 105–124. Academic Press, New York.

Wagner, G. P. (1989). The origin of morphological characters and the biological basis of homology. *Evolution* 43, 1157–1171.

Wake, D. (1994). Comparative terminology. *Science* 265, 268–269

Weiss, P. (1923). *Naturwissen.* 11, 669 [quoted in Weiss, P. (1939). ''Principles of Development'' Holt, New York].

Weiss, P. (1939). ''Principles of Development.'' Holt, New York.

Wilder, E. L., and Perrimon, N. (1995). Dual functions of wingless in the *Drosophila* leg imaginal disc. *Development* 121, 477–488.

Williams, J. A., Paddock, S. W., Vorwerk, K., and Carroll, S. B. (1994). Organization of wing formation and induction of a wing-patterning gene at the dorsal–ventral compartment boundary. *Nature* 368, 299–305.

Wilson, E. B. (1896). ''The Cell in Development and Inheritance.'' Macmillan Co., New York.

Wilson, E. B. (1898). Cell lineages and ancestral reminiscences. *In* ''Biological Lectures from the Marine Biological Laboratories, Woods Hole, Masssachusetts,'' pp. 21–42. Ginn, Boston.

Yang, Y., and Niswander, L. (1995). Interaction between the signalling molecules WNT7a and SHH during vertebrate limb development: Dorsal signals regulate anteroposterior patterning. *Cell* 80, 939–947.

Received for publication April 18, 1995
Accepted October 24, 1995