

# **Embryos, Genes, and EVolution**

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## **The Developmental-Genetic Basis of Evolutionary Change**

**Rudolf A. Raff and Thomas C. Kaufman**

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**Macmillan Publishing Co., Inc.**  
New York  
**Collier Macmillan Publishers**  
London

# Preface

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This book has its immediate origins in a course we have taught for the past several years at Indiana University on the developmental-genetic mechanisms that generate evolutionary changes in morphology. The underlying theme that evolution cannot be understood without an understanding of the developmental processes that produce form in ontogeny is an old one; indeed, in the late nineteenth century it was a dominant part of evolutionary theory. However, throughout most of the twentieth century the obvious connection between phylogenetic transformations in shape of organisms and the underlying modifications of the genetic systems controlling ontogeny has been largely ignored except by a few outsiders to the neo-Darwinian synthesis, which was built of other elements. That synthesis was incomplete.

Our own fascination with this subject goes back to our undergraduate days, in which we were first exposed to the incredible diversity of body plans of marine invertebrate phyla and to the elegant functional anatomy of vertebrates. Equally important, both of us, in our research, have been engaged in somewhat different ways in trying to determine how genes direct the processes that make up embryonic development. Thus, there is a distinct mental set to our approach to evolution as there is to our approach to development, and this colors our choice of the topics considered in this book. The essential position is that there is a genetic program that governs ontogeny, and that the momentous decisions in development are made by a relatively small number of genes that function as switches between alternate states or pathways. The significance of this view, if correct, is that evolutionary changes in morphology occur mechanistically, as a result of modifications of these genetic switch systems. If our prediction that there are a relatively small number of such gene switches is correct, then the potential exists for geologically rapid and dramatic evolutionary changes. Such macroevolutionary events are apparently associated with the origins of new groups of organisms.

The text is divided into four informal sections. The first group of chapters deals with the history of the problem, with rates of evolution, and with the noncongruence of morphological and molecular evolution. The second set of chapters deals with the evolutionary role of developmental processes and considers the organization of eggs and early embryos, interactions between regions of embryos, and timing. Change in relative timing of developmental processes provides one of the best-documented mechanisms for achieving evolutionary changes in shape. Indeed, most previous treatments of the role of developmental processes in evolution, notably those of de Beer and Gould, have focused

on timing. Other modes of disassociating processes with respect to one another have been discussed less frequently, but may be of equal importance. The third part of the book considers the genetics of development; and here we demonstrate that genes indeed control ontogeny in very specific ways and that there is a genetically determined developmental program. Finally, although ontogeny can be analyzed by classic genetic methodology, we are not limited to this approach in the analysis of gene expression. Advances in techniques for the cloning of genes and for high-resolution studies of DNA and RNA have made it possible to examine directly genes and gene expression during development. The results of such studies are discussed in the remaining chapters. In the final chapter we attempt to arrive at a synthetic integration of the developmental-genetic basis for morphological evolution.

One other point of organization should be mentioned. To avoid annoying interruptions of the flow of the text by intrusive citations or footnotes, we have worked most references into the text by author name without dates. This procedure provides sufficient information to locate the cited work in the bibliography at the end of the book.

As in any project of this kind, the advice and support of many people have been vital. We are grateful to our many colleagues who patiently answered our numerous questions and provided us with information, references, reprints, preprints, sketches, and photographs. We also thank the students who have studied this problem with us in our course for their perceptive questions and for insights they have provided. We owe particular thanks to our colleague Elizabeth C. Raff, who so superbly illustrated this book and who so mercilessly red-penciled the awkward writing of our first drafts.

Because so many of the topics we have had to consider fall well beyond the range of our own expertise, it has been especially important to us that the chapters be critically read by experts. These readers generously put forth considerable time, effort, and thought in their reviews and provided us with priceless criticism and suggestions as well as very much appreciated encouragement. To John Tyler Bonner, Péter Bryant, Hampton Carson, Robert Edgar, Gary Freeman, Stephen J. Gould, Donna Haraway, Vernon Ingram, Burke Judd, Raymond Keller, William Klein, Jane Maienschein, Elizabeth Raff, Steven Stanley, Alan Templeton, Robert Tompkins, David Wake, and J. R. Whittaker we are profoundly grateful. Naturally, like all good academics, we have not followed all of the advice proffered—and no doubt we have committed errors for which only we can accept responsibility.

We have been fortunate in having our manuscript skillfully typed by Ann Martin and in having the help of Monica Bonner, who with extraordinary patience, good spirits, and intelligence kept us from being submerged by organizational problems. We also owe much to the staffs of the libraries of Indiana University and the Marine Biological Laboratory at Woods Hole, Massachusetts for their help in locating materials and for their forbearance with holders of long-overdue books.

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# One

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## Embryos and Ancestors

"Perhaps I ought to explain," added the badger, lowering his papers nervously and looking at the Wart over the top of them, "*that all embryos look very much the same. They are what you are before you are born—and, whether you are going to be a tadpole or a peacock or a cameleopard or a man, when you are an embryo you just look like a peculiarly repulsive and helpless human being. I continue as follows:*

The embryos stood in front of God, with their feeble hands clasped politely over their stomachs and their heavy heads hanging down respectfully, and God addressed them. He said: 'Now, you embryos, here you are, all looking exactly the same, and We are going to give you the choice of what you want to be. When you grow up you will get bigger anyway, but We are pleased to grant you another gift as well. You may alter any parts of yourselves into anything you think would be useful to you in later life.'"

*T. H. White, The Once and Future King*

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## The Problem of Morphology

Organisms have morphologies, and they exhibit behaviors and physiological adaptations. In our perspective of long eons of geological time these characteristics appear to be almost protean: the lobe-fin of the crossopterygian becomes the limb of the amphibian, the wing of a bird, the human arm and hand. This is the visible record of evolution. By what mechanisms are evolutionary changes in morphology achieved?

In fact, we already know the answer to this question, at least in a formalistic sense. Garstang provided it in 1922 when he pointed out that an evolutionary sequence or phylogeny is not simply a succession of adult forms. Each generation of adults has been produced by a series of developmental processes, ontogeny, from an apparently structureless egg to the complex morphology of the adult. Thus, in order for an evolutionary change to be expressed as an altered body structure, a new morphology, a change, must occur in ontogeny.

One might expect that the role of developmental processes in evolution should be a major component of current studies of evolution; however, this is not so. Embryological development, which was so vital a part of evolutionary theory in the late nineteenth century, has been considered largely irrelevant in the twentieth. Later in this chapter we shall discuss the reasons for this strange divorce. Of course, apprecia-



tion of the significance of the relationship between development and evolution never totally died out. Garstang, J. S. Huxley, de Beer, and Goldschmidt all explicitly dealt with this relationship in a serious way during the period from the 1920s to the 1950s. And the recent publication of Gould's book *Ontogeny and Phylogeny* indicates that current interest in the subject may be not only alive, but lively as well.

Our own fascination was stimulated several years ago by reading de Beer's book *Embryos and Ancestors*, which so cogently argues that changes in timing of developmental events can have dramatic evolutionary results. Unfortunately, beyond a brief general discussion of genes controlling rates of developmental processes, de Beer paid little attention to the role of genetic regulation in development or evolution. There was simply not enough known about developmental genetics when de Beer wrote the first edition, published in 1930, for him to have dealt with it in a very profound way. By 1958, when the third and last edition of *Embryos and Ancestors* was published, much more was known, but de Beer cited little of the advances in developmental genetics made subsequent to the 1930s. His main emphasis lay in another direction.

In fact, the developmental-genetic basis for evolutionary change has simply never been explored in detail. This is what we intend to accomplish in this book. Our premise is that developmental processes are under genetic control and that evolution should be envisaged as resulting from changes in the genes regulating ontogeny.

It is interesting that this was the view advanced by Goldschmidt in 1940 in his *Material Basis of Evolution*, though not enough was known about genes and their functions in development at that time for the synthesis to be successful. Goldschmidt's ideas have been ignored for the past 35 years because of his idiosyncratic (and erroneous) view of the nature of genes, but his definition of evolution provides a perfectly clear statement of the theme of this book:

*Evolution means the transition of one rather stable organic system into a different but still stable one. The genetic basis of the process, the change from one stable genetic constitution to another, is one side of the problem. No evolution is possible without a primary change within the germ plasm; i.e., predominantly within the chromosomes, to a new stable architecture. But there is also another side to the problem. The germ plasm controls the type of the species by controlling the developmental process of the individual... the specificity of the germ plasm is its ability to run the system of reactions which make up the individual development, according to a regular schedule which repeats itself, ceteris paribus, with the purposiveness and orderliness of an automaton. Evolution, therefore, means the production of a changed process of development, controlled by the changed germ plasm....*

The term germ plasm used by Goldschmidt refers to the genetic material—in modern terms, the DNA of the genome.

What sorts of genes govern ontogeny, and by what modes do they evolve?

At present the best-understood genes are those that code for specialized RNAs or proteins vital to the overall structure and function of cells, such as ribosomal RNAs; various enzymes; structural proteins, such as tubulin or collagen; or carrier proteins, such as hemoglobin.

Estimations of the relevance of such structural genes to the control of development and morphogenesis span a considerable range. Our view is that structural genes have a very limited regulatory function in development, but the opposite has been suggested. An example of a developmental hypothesis granting an extensive role to structural genes and their products is that advanced by Monod in *Chance and Necessity*. Monod proposed that the generation of structural complexity results from what he called the molecular epigenesis of proteins. By this term he was referring to a well-known feature of proteins, that the amino acid sequence of a protein determines the three-dimensional conformation the protein assumes within the environment of the cell. Further, proteins interact with other proteins in specific ways to yield supramolecular structures. To quote Monod, "Order, structural differentiation, acquisition of functions—all these appear out of a random mixture of molecules individually devoid of any activity, any intrinsic functional capacity other than that of recognizing the partners with which they will build the structure." He goes on to suggest that this process both underlies and serves as a paradigm for a series of autonomous epigenetic events culminating in the development of the entire organism. An extreme interpretation of this idea may conjure up the epigenetic fantasy that, given a mixture of the proper macromolecules, it would be possible to obtain the assembly of a mouse from solution.

Monod's proposal, even stopping short of the extreme, is untenable as a model for development. Nor does evolution of structural genes account for morphological evolution. The work of A. C. Wilson and his collaborators indicates that, at least with respect to living groups of organisms such as frogs and mammals, evolution of structural genes for proteins is largely irrelevant to morphological evolution. Humans and chimpanzees have rapidly diverged morphologically, but they are 99% similar in their protein sequences. On the other hand, frogs, an old group, have exhibited rather slow morphological rates of evolution, but their protein sequences have evolved at rates comparable to those of other organisms. This realization has led King and Wilson to propose that changes in regulatory genes rather than structural genes provide the basis for morphological evolution.

Because there is a hierarchy of interacting controls governing gene expression and ontogeny, regulatory genes fall into a number of categories and are more difficult to define as a group than structural genes. Essentially, structural genes supply the materials for development and regulatory genes both provide and interpret the blueprint. Structural genes are relatively easy to understand because the products they code for can be readily isolated and studied, and their functions defined. Not surprisingly, regulatory genes have proven a great deal more elusive than structural genes. Some regulatory genes, or elements, produce no products; others do, but their products exist only in minute amounts. The best-known example is the lac-repressor protein of the bacterium *E. coli*. This product of a regulatory gene controls the expression of the genes involved in lactose metabolism. Only 10 molecules of repressor are present per cell.

Regulatory genes function throughout the developmental process and govern ontogeny in three major ways: first, by controlling the timing of events; second, by making binary choices, and thus decisions about the fates of groups of cells or regions within the embryo; and third, by integrating the expression of structural genes to produce stable, differentiated tissues. All three modes of regulation have a considerable bearing on evolution.

That changes in timing of developmental events serve as a major and flexible mechanism for achieving significant morphological evolution was argued by de Beer in his seminal work *Embryos and Ancestors* and more recently by Gould in *Ontogeny and Phylogeny*. These authors were less concerned with mechanisms for the genetic control of developmental processes than with defining the kinds of modifications possible in relative timing of events in ontogeny and in demonstrating their evolutionary sequels. A variety of evolutionary events have been proposed as representing consequences of timing changes. The most widely cited are cases of neoteny in which new kinds of adult body plans result from larval stages becoming sexually mature and losing the ancestral adult stage. We explore timing as a mode of regulatory evolution in Chapter 6.

However, genetic regulation of ontogeny is not limited to control of timing. Recent work, especially with the fruit fly, *Drosophila melanogaster*, which has become something of a eucaryotic *E.coli* to investigators of gene organization and function in this decade, has revealed that a hierarchy of regulatory genes control the organization of the developing embryo. These genes act as switches that determine which of two alternate choices a cell or group of cells will make in development. Once the decision is made, the cells are restricted in which subsequent choices they can make as their developmental fates become further specified. Regulatory genes of this type are accessible to study because of the spectacular effects manifested by mutations that abolish or modify their functions as binary switches. In *Drosophila* these mutations produce transformations in which a modified pattern of morphogenesis will substitute one structure for another, such as legs in place of antennae or an extra set of wings instead of halteres. Modification or creation of new sets of this class of regulatory gene provide an impressive potential for production of radical evolutionary modifications or morphological novelties. That such a mode of evolution has occurred, and indeed has been critical in the evolution of insects and other organisms, is clear, and we have much more to say about it later in Chapters 8 and 9.

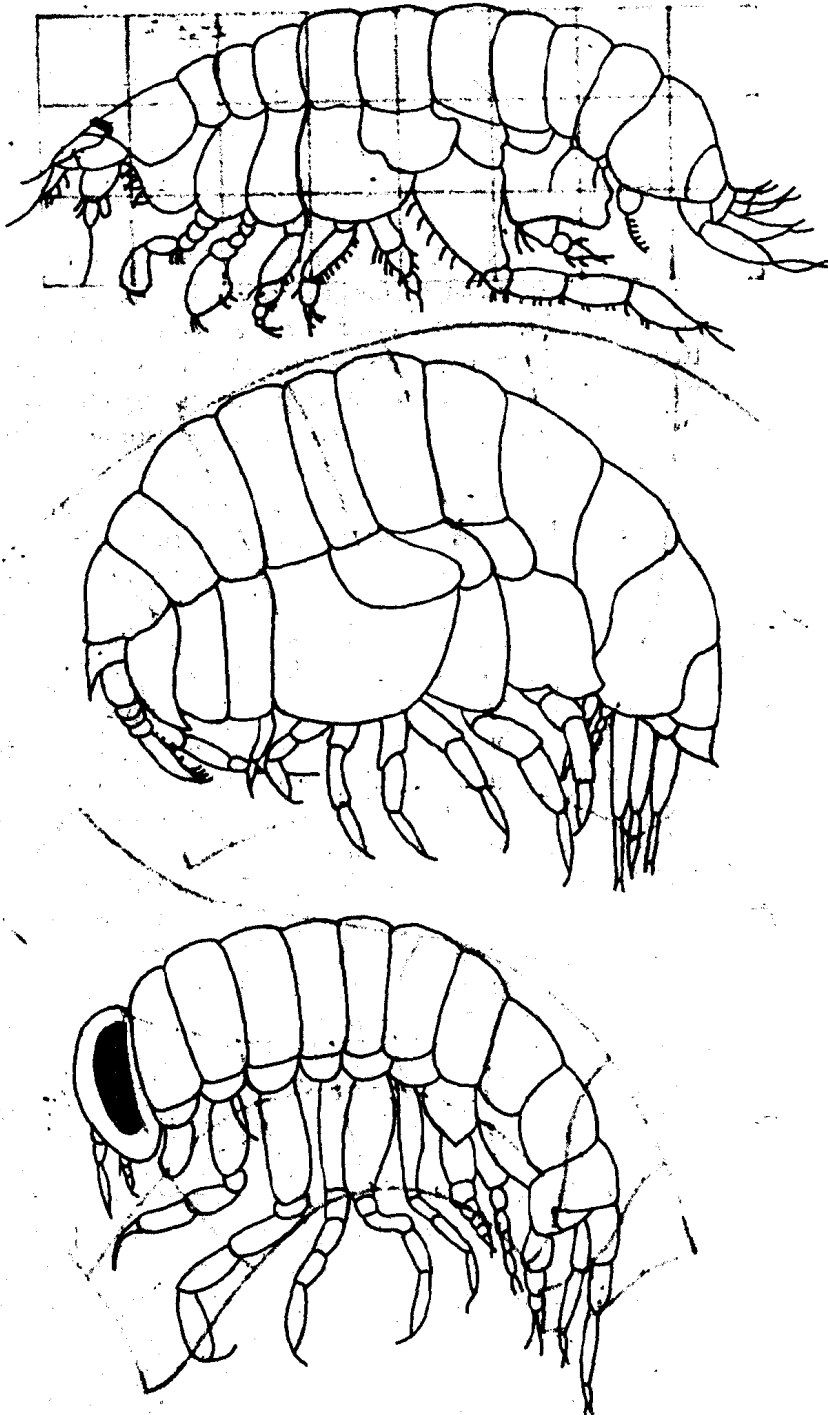
Like changes in timing or organizational integration, changes in regulatory genes controlling tissue differentiation have great evolutionary potential. Whereas changes in the first two classes of regulators yield changes in morphology, changes in the third class produce novel tissues. An example that we discuss in greater detail in Chapter 12 is the mammary gland, the evolution of which has involved the origin of a new tissue, novel proteins, new regulatory genes, and a set of behavioral patterns crucial in the evolution of mammalian reproduction and infant care.

The three modes of regulation of development we have so briefly outlined do not stand apart from each other. All have been involved in varying degrees in the morphological evolution of particular lineages of organisms.

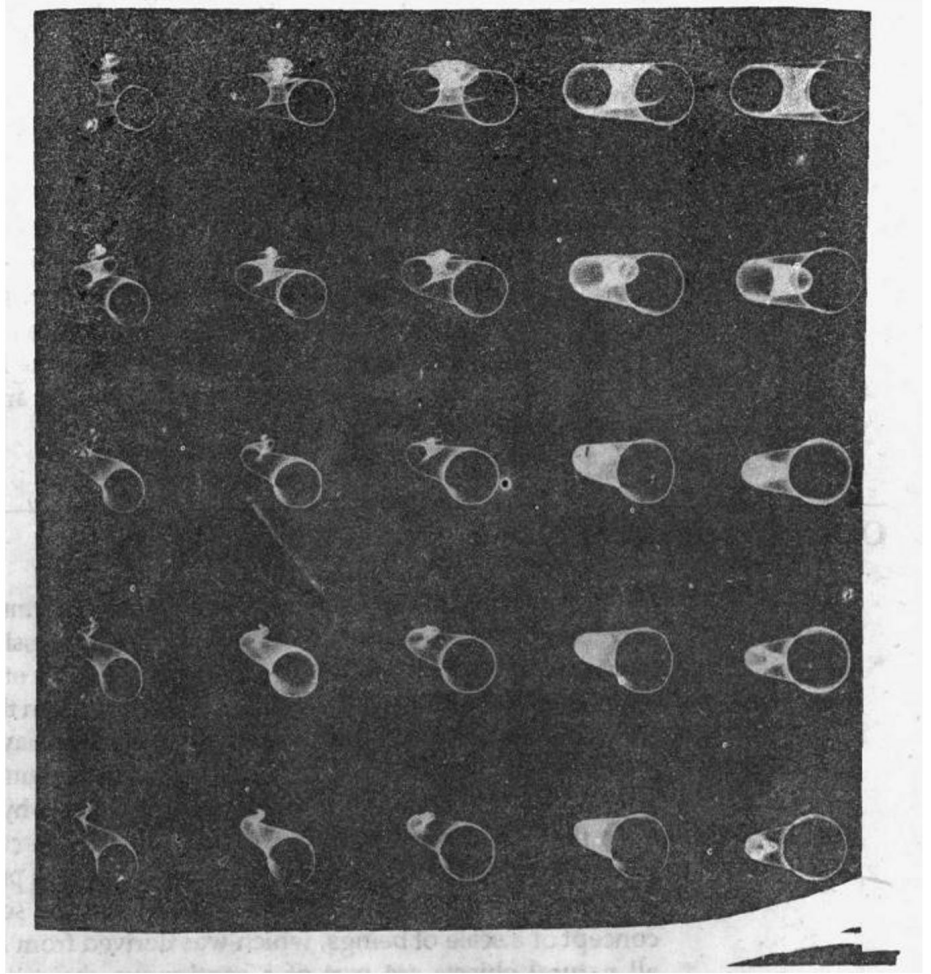
Perhaps the major difficulty we face in our project of attempting to understand morphological evolution in terms of developmental-genetic mechanisms is that the generation of morphology is extremely poorly understood at the molecular level. This is true not only from the perspective of mechanisms of morphogenesis per se—cell motility, cell-cell interactions, and pattern formation—but also because of a conceptual difference in the ways in which we score the information content of morphological structure as opposed to genetic information. As an illustration of this difference consider some approaches taken to morphogenesis from a nonmolecular genetic point of view by D'Arcy Thompson, who pioneered the application of mathematics to problems of shape in his book *On Growth and Form* first published in 1917 (Fig. 1-1). His aim was simple: "We want to see how, in some cases at least, the forms of living things, and the parts of living things, can be explained by physical considerations, and to realize that in general no organic forms exist save such as are in conformity with physical and mathematical laws." Thompson made his point in a book that has enlightened generations of biologists, who have learned from it the mathematical rules that underly the shapes of interfaces between cells and the morphologies of radiolaria or spiral shells and rams' horns; why the vertebrate skeleton and bridges obey the same laws of engineering; and how by using transformations of Cartesian grids, it is possible to represent the evolutionary changes of shapes of complex objects, such as skulls, fishes, and isopods. Thompson removed the sense of ineffable mystery from biological form, and indeed, elegantly showed that complex biological entities obey analyzable physical and mathematical rules. However, he paid little attention to genetic or molecular events, perhaps wisely, because these are still not completely understood, and instead focused on physical forces acting on the organism as immediate causes of morphology.

Thompson was much less successful in dealing with changes in shape during growth. Mathematical analysis of relative growth of the parts of an organism during its development (allometry) was devised by Huxley in the early 1930s. Basically, such growth relations can be expressed by the simple expression  $y = bx^a$ , where  $x$  and  $y$  represent dimensions of two structures being compared. Allometry has been of considerable value in understanding evolutionary changes, but again, a genetic or molecular appreciation of the alterations in bodily proportions that accompany growth remains elusive and is assuredly more complex than the simple allometric equation implies.

Similarly, computer simulations of mollusk shells, produced by Raup and Michelson, show that the generation of objects with quite sophisticated morphologies may require only a small number of parameters (Fig. 1-2). For example, snail shells are tapered tubes wound in a spiral about a fixed axis. Only four parameters are required to generate com-



**FIGURE 1-1.** Transformations in the shapes of some isopods. The species at the top of the figure is projected onto rectangular coordinates. Deformations in the corresponding grids for the two other species illustrate evolutionary changes in proportions. [Redrawn from D. W. Thompson, *On Growth and Form*, Cambridge University Press, Cambridge, 1961, p. 295.]



**FIGURE 1-2.** Computer simulation of the forms of coiled shells. Rate of translation along the axis increases to the left while the rate of expansion of the generating curve increases from top to bottom. The shape of the generating curve and the distance between the generating curve and the coiling axis are the same in all. [Photograph courtesy of D. M. Raup, from D. M. Raup and A. Michelson, *Theoretical morphology of the coiled shell*, *Science* 147:1294-1295, 1965. Copyright 1965 by the American Association for the Advancement of Science.]

puter analog simulations of actual shells; these are (1) cross-section shape of the generating curve, (2) rate of expansion of the generating curve with respect to revolution, (3) position and orientation of the generating curve relative to the axis, and (4) rate of movement of the generating curve down the axis. These simple parameters describe the shape to be generated, but they bear little relationship to the genetic program or the actual mechanisms by which organisms read out the genetic program for morphogenesis.

Although organisms obey the laws of chemistry and physics, there is an additional factor governing morphology, the evolutionary history of the organism. As elegantly pointed out by François Jacob, evolution operates by tinkering. New structures do not appear *de novo*; rather, evolution produces novelties by modifying already existing systems or

structures. The first vertebrates, the fishlike Agnatha, were jawless. The origin of jaws, one of the great advances of vertebrate evolution, involved the transformation of an anterior pair of gill arches into primitive jaws. Similar conversions of preexisting structures have been shown in the evolution of specialized limbs, such as wings of pterodactyls, birds, and bats, or the origin of the bones of the inner ear of mammals from remnants of reptilian jaw articulation.

Because ontogenetic processes are highly integrated, they tend to be extremely conservative and stable. Thus, ontogeny and morphogenesis not only obey physical laws, as indeed they must, but also reflect the evolutionary history of the process. Historical accident and the necessity of maintaining integration clearly place limits on the kinds of evolutionary changes possible in the developmental process and thus constraints on morphological evolution.

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## Ontogeny, Phylogeny, and Recapitulation

In *Through the Looking-Glass* the White Queen informs Alice that "Why, sometimes I've believed as many as six impossible things before breakfast." To the modern reader the history of ideas about the relationship of ontogeny to evolution has very much the same flavor, yet the ideas we may currently recognize as absurd have had a profound effect on our perception of evolutionary mechanisms. How tenacious, after all, is the slogan "Ontogeny recapitulates phylogeny"?

To the transcendentalists of the early nineteenth century there was a fundamental unity of life, which was expressed as a parallel between the embryonic development of the individual and the scale of beings. The concept of a scale of beings, which was derived from Aristotle, held that all natural objects are part of a continuous chain that links inorganic creation with a series of increasingly complex living forms. Inanimate nature grades into plants, then simple animals such as sponges, to insects, fishes, birds, mammals, and finally, humans. This scheme was static and should not be construed as evolutionary in nature: It simply represented God's plan of creation. According to the law of parallelism, which is generally known as the Meckel-Serres law, after its two chief proponents, J. F. Meckel in Germany and Étienne Serres in France, a higher animal in its embryological development recapitulates the adult structures of animals below it on the scale of beings. Conversely, lower animals represent the permanent larval stages of more advanced forms.

Meckel, according to Russell, was a "timid believer in evolution," and indeed his final (1828) statement of the law of parallelism was cast in evolutionary terms:

*The development of the individual organism obeys the same laws as the development of the whole animal series; that is to say, the higher animal, in its gradual evolution [ontogeny], essentially passes through the permanent organic stages which lie below it; a circumstance which allows us to assume a close analogy between the differences which exist between the diverse stages of development, and between each of the animal classes.*

1407-20

However, as with the scale of beings, there was nothing inherently evolutionary about the law of parallelism. It too could be visualized as representing a divine plan of creation. This was the view of Louis Agassiz, who was to become a bitter opponent of Darwin. Agassiz, the discoverer of the Ice Age and the world's foremost authority on fossil fishes, extended the law of parallelism to the fossil record. By 1849 there were sufficient paleontological data available that Agassiz could demonstrate a three-fold parallelism such that a higher organism in its development passed through stages resembling not only the adults of a series of lower related forms, but also the progression of fossils of its class in the geological record. Agassiz, of course, unlike the transcendentalists, fully appreciated that Cuvier's classification had swept away a single scale of beings. Rather, there were, according to Cuvier (1812), four fundamentally different modes of body organization among animals: vertebrates, mollusks, articulates, and radiates. Recapitulation or parallelism could only exist within a class.

It was in the climate of the transcendentalist biology of the 1820s that von Baer carried on the studies of animal development that largely introduced embryology as a science. The magnitude of von Baer's achievements in embryology can be gauged by considering that he discovered the mammalian ovum and the notochord and that he formulated the theory of germ layers. His interpretations of his studies in comparative embryology led to a series of generalizations that made nonsense of the idea that animals in development recapitulate the scale of beings. Von Baer, like Cuvier, noted that instead of a single scale there were four basic plans of body organization. Development clearly reflects these basic plans. For example, the notochord and neural tube characteristic of vertebrates arise early in development, and thus, "The embryo of the vertebrate animal is from the very first a vertebrate animal, and at no time agrees with an invertebrate animal." Vertebrate embryos resemble only other vertebrate embryos, and von Baer denies resemblance to adults or anything else: "...the embryos of the Vertebrata pass in the course of their development through no (known) permanent forms of animals whatsoever."

Von Baer published the following major generalizations, his famous laws, in 1828:

1. *That the more general characters of a large group of animals appear earlier in their embryos than the more special characters.*
2. *From the most general forms the less general are developed, and so on, until finally the most special arises.*
3. *Every embryo of a given animal form, instead of passing through the other forms, becomes separated from them.*
4. *Fundamentally, therefore, the embryo of a higher form never resembles any other form, but only its embryo.*

These empirical laws retain their validity today and may be observed in operation in the development of any vertebrate, such as von Baer's favorite research organism, the chick. Early in development the chick embryo can be recognized only as a vertebrate, because early embryos of



all classes of vertebrates are nearly identical; somewhat later it can be recognized as a bird; and only later still can it be recognized as a chick.

While von Baer's laws made the idea of recapitulation of the chain of being untenable, they were not, as pointed out by Ospovat as well as by Gould, really incompatible with a modified form of recapitulation, and in fact were to be eventually absorbed by Haeckel in his scheme of evolutionary recapitulation. The reason is not difficult to find. Von Baer's concept of development was progressive. Embryos pass from the general and simple to the specific and complex. Resemblances between embryos of higher forms and adults of lower forms exist, and are a necessary consequence, in von Baer's view, of two factors. Von Baer observed that the degrees of morphological complexity and differentiation, which characterize higher organisms as opposed to lower, coincided with the increasing histological and morphological complexity seen in the course of individual development. Thus, although von Baer realized that embryos of higher animals do not recapitulate the adult stages of lower forms, they do resemble them in complexity. To the modern reader this may sound contradictory to von Baer's fourth law, but von Baer himself explained that, "It is only because the least developed forms of animals are but little removed from the embryonic condition, that they retain a certain similarity to the embryos of higher forms of animals." The second factor is related. Von Baer held that primitive forms more closely resemble the hypothetical archetype, or idealized basic form, for a particular plan of body organization. Adult fishes are thus nearer the basic type than adult mammals: Both resemble the vertebrate archetype early in ontogeny, but mammalian development diverges farther from it than does that of the fish (Fig. 1-3).

While the concept of the archetype, which is a part of the transcendentalist approach to biology, would seem to be of little appeal to Darwin and his followers, it in part continued to exert a considerable influence on the interpretation of embryological facts. The importance of embryological data to late-nineteenth-century evolutionists was their phylogenetic content. The three-fold parallelism of Agassiz and the generalizations of von Baer were recast in evolutionary terms.

Darwin wrote in the 1859 edition of *On the Origin of Species* that "in the eyes of most naturalists, the structure of the embryo is even more important for classification than that of the adult. For the embryo is the animal in its less modified state; and in so far it reveals the structure of its progenitor." The archetype is here visible to Darwin as it was to von Baer. But of course Darwin made different use of the idea than did von Baer, who remained skeptical about evolution until his death in 1876. According to Darwin,

*In two groups of animals, however much they may at present differ from each other in structure and habits, if they pass through the same or similar embryonic stages, we may feel assured that they have both descended from the same or nearly similar parents, and are therefore in that degree closely related. Thus, community in embryonic structure reveals community of descent.*

Darwin also suggested that an evolutionary rationale could also be made for the three-fold parallelism: "As the embryonic state of each species