Seeds of Change in Embryonic Development

Physical constraints inherent in embryonic development may contribute more to evolutionary change than recent theory has allowed

Embryos, and the processes of development that shape them on their way to adulthood, are being welcomed back into the study of evolutionary biology after a long period of considerable neglect. This was the principal conclusion that emerged from a recent conference on evolution and development arranged by Dahlem Konferenzen in West Berlin.*

The main thrust of the argument is that although natural selection may be the major force molding life's diversity, it is by no means the only important factor involved. Fundamental laws underlying the developmental process limit in important ways the raw material—morphological novelties—upon which selection acts. In other words, because embryological development is constrained so that some physical forms are possible while others are not, the direction of evolutionary change is influenced first by developmental constraints and only then by natural selection.

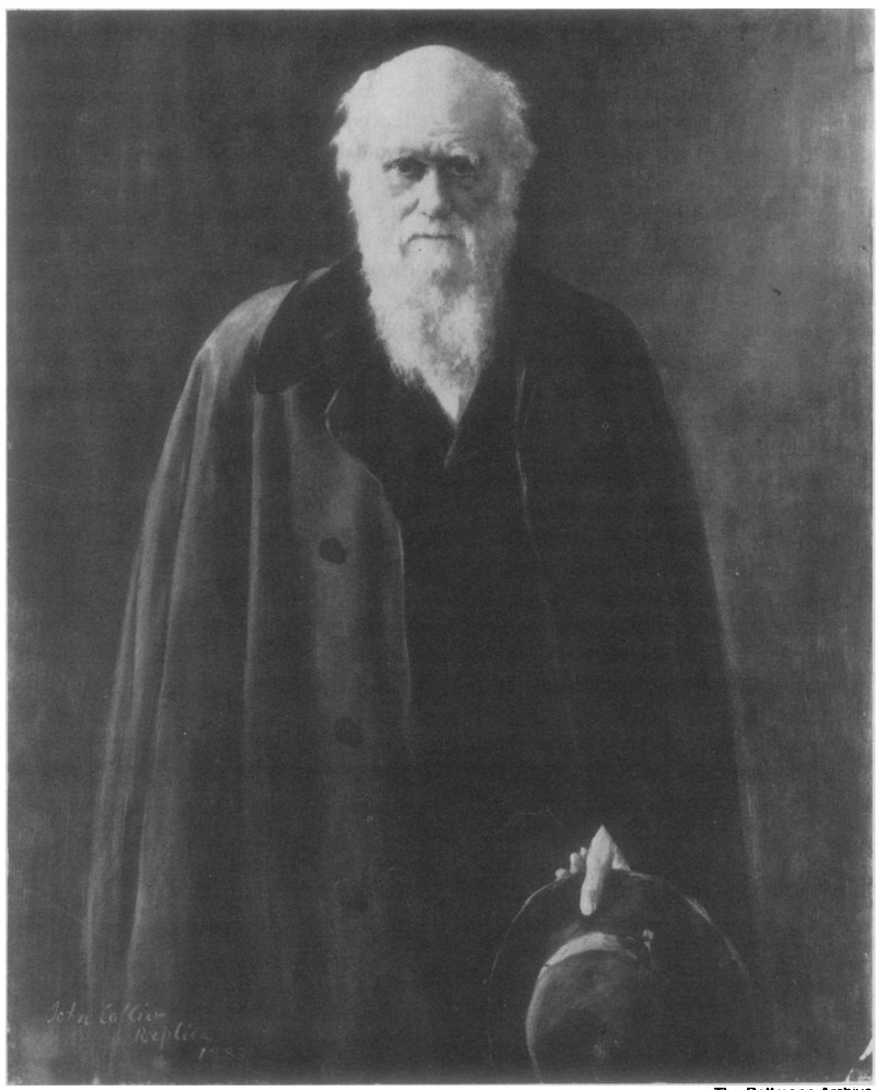
Darwin would have been happy with this pluralistic view of evolution, but it is somewhat at odds with the almost exclusively selectionist position that has prevailed for the past several decades.

The intellectual antecedent of the Dahlem meeting was the macroevolution conference held last fall in Chicago (*Science* 21 November 1980, p. 883). That conference posed the question, what class of mechanism is responsible for the major shifts in evolution? The Berlin meeting addressed the same issue, but sought to hone the questioning by focusing on development and by including molecular biologists in the discussions.

As things turned out, there were two identifiable divisions. The first separated those who believe that the genome is capable of generating a virtually unlimited array of morphological variation, from others who consider morphological variation to be significantly restricted by developmental processes. This latter, as indicated earlier, emerged as the majority view. The second division concerned the contribution of molecular biology to the understanding of development and thus to constraints on evolutionary change. Some considered molecular biology to be the most direct route to understanding development, while others thought that such molecular detail is too far removed from the organism to offer any useful insight into the process. This latter view prevailed.

Diverse though life is, there are distinct gaps in morphological space: there are, for instance, no animals with wheels instead of legs, nor ones festooned with a cross between hairs and feathers. Why? "The gaps are there," said Antonio Garcia-Bellido, a geneticist from Madrid, "because of a failure of the genes to fill them." In other words, given sufficient time and opportunity, all physical forms are possible. For David Wake, of the Museum of Vertebrate Zoology, the University of California, Berkeley, Garcia-Bellido's statement was "the focus of our differences." The differences with Garcia-Bellido's position were in fact twofold: not only does the Spanish geneticist consider that virtually all morphological variation is possible, but also that the answers to development are to be discovered in the genes. Not all the molecular biologists at the meeting agreed with the first point, though they supported the second.

Wake, and many other non-molecular biologists, believes that the processes of development impose real barriers on what is structurally feasible. The gaps in morphological space, according to this



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Charles Darwin

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*Conference proceedings will be available in November from Dahlem Konferenzen, Wallotstrasse 19, D-1000 Berlin 33, West Germany.

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view, are there, not because the genes have so far failed to fill them or, having filled them, natural selection has wiped them out, but because there are fundamental laws of biological form that limit available options.

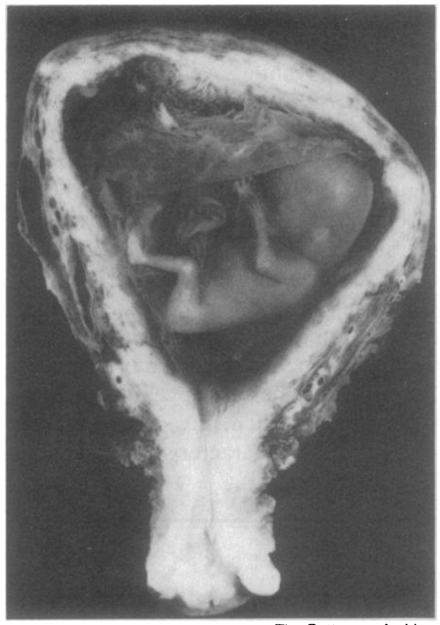
So, the first position sees the origin of morphological novelties as the result of an open-ended tinkering with the genes in evolutionary time. The second looks to higher levels of explanation, levels above the genome, for an understanding of evolutionary change.

It is a truism to say that an organism and its genome are inseverably linked: the one leads consistently to the other. The question is, how does this truly astonishing translation take place? What is written in the genome of an ant that makes it give rise to an ant and not an elephant?

If the messages in the genes can be regarded as a program that directs development so as to create an adult form, detailed information about genome structures will reveal how organisms are formed and how novelties arise. Gunther Stent, of the University of California, Berkeley, who has recently turned away from molecular biology to devote himself to the study of development, argued against this. If there are no such developmental programs in the strict sense, and instead the patterns of development are set by the interactions of molecules, cells and tissues, then, he argued, "to say that the differences between organisms lies in the differences between their genomes has no explanatory value."

In the 1930's and 1940's there was a vogue for studying heredity in terms of the interatomic forces that governed the behavior of the atoms that made up genetic material. As it transpired, although atomic forces are undoubtedly crucial in the physicochemical properties of genes, their function was eventually described at a higher, macromolecular level. "Similarly," says Stent, "the insights into developmental mechanisms thus far available suggest that solutions to the problem of development lies at a cellular rather than a genetic level although genes will undoubtedly figure in some crucial part, but only a part, of the solution."

There was much discussion about what exactly constitutes a program, provoked partly by the content of the exchanges and partly by the pugnacious, though good-natured, tone in which Stent presented his argument. ("I'm doing this for your mental hygiene," he explained.) The formation of proteins is programmatic, Stent allowed, because there is a one-to-one correspondence between the arrangement of bases in the DNA and the sequence of amino acids in the primary structure of the protein molecule. The subsequent folding of the polypeptide chain, contends Stent, is not programmatic as it is a consequence of the environment in which the molecule finds itself. The same can be said of the interaction between different protein molecules that are synthesized in a coordinated manner in a developing embryo, runs the argument.



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The secret of evolution lies with the embryo.

Stent's tight definition of what is programmatic and what is not drew instant accusations of semantic polemics. He rejected the charge and said that the contribution of the molecular biologists at the meeting demonstrated that those people who do view development as programmatic "see their goal as the discovery of the program structure in the genome, as embodied in the genome structure." Stent claimed that studies of the development of the nervous system have shown that the notion of genetic programming is not only defective at the conceptual level but also "misrepresents the knowledge already available from developmental studies."

Some developmental biologists responded enthusiastically to this notion, because it releases them from what they perceive as the tyranny of molecular biology. Wake, an evolutionary biologist, warmed to its appeal because it accords with some of his observations. For instance, in some groups of salamanders the bones of the upper jaw develop early, thus producing in these species a wide head. Other species have very narrow heads because growth of these same bones is scheduled much later in development and so they are relatively small. "I'm sure the timing of the expression of certain genes underlies this difference," says Wake, "but if all you knew was the sequence of expression of the genes you would know nothing about how the shape of the head is determined. If I were to ask Igor Dawid [a molecular biologist at the National Institutes of Health] how does the genome do these things? he would say he doesn't know. But he's sure the genome is the place to look for the answers."

Dawid, who was the rapporteur of the molecular biology group at the Dahlem meeting, concedes shortcomings in the science. "Even if, for instance, we knew the total sequence of the human genome, we wouldn't know what a human being looked like," he says. And in its meeting report, the molecular biology group recognizes that "the present understanding of genome function is not sufficient to make a large contribution" to the study of morphological evolution. "But," continues the report, "we have learned certain properties of genome organization and function that provide a framework of generally useful information" (see, for instance, *Science* 7 August, p. 634).

Eric Davidson, of the California Institute of Technology, was even more bullish about the utility of molecular biology in analyzing evolutionary change. "The thing that evolves, the thing that's different between species, is the genome," he states. "There's no question that a knowledge of genome structure and an understanding of how genes are regulated, especially in development, will tell us a great deal about evolutionary mechanisms." This view must be correct, within certain limits.

Nevertheless, the black box nature of the relationship between genome and organism was emphasized by Wake's citation of further information on salamanders. There are many species of salamanders, some of which are physically very similar. "Two of them are virtually indistinct morphologically," says Wake. "Electrophoretic tests on 30 or so proteins show a wide genetic distance between the two species, and this is consistent with the fact that, by current estimates, the species separated some 65 to 70 million years ago." The wide genetic distance in some important proteins is, however, cause for thought, says Wake. "For many years evolutionary biologists have equated morphological similarity with close genetic relationship. This is clearly not necessarily the case."

What must be the case, however, is that whatever genetic mechanisms are responsible for shaping these species' physical appearance have remained stable over millions of years.

According to classic population genetics (which was not represented at the Dahlem meeting), evolutionary separation between two populations arises through the continual selection of traits which leads to changes in gene frequencies. In the majority view of the Dahlem meeting, however, the focus of evolutionary modification is the developing embryo, a dynamic growing entity in which a small alteration at an early stage can produce disproportionately large shifts in morphology in the adult, often affecting many parts of the body. Evolutionary change in this case, therefore, has to do with the modification—perhaps very minor modification—of genetic regulatory systems, genes that affect the timing of developmental processes. For instance, it is thought that a small adjustment of the developmental clock could account for many of the important physical differences between humans and our closest relative, the chimpanzee.

The idea that small differences in the timing of development might generate large shifts in physical form receives much observational support. "Numerous examples have been documented in modern and fossil faunas," notes one of the group reports. This being so, the mechanisms is "an evolutionary force in its own right and not just a contributor to the random pool of imperceptible variation that makes natural selection the only force of evolutionary change," comments Stephen Jay Gould, of the Museum of Comparative Zoology, Harvard University.

The challenge now is to identify the putative laws of development that might constrain and offer opportunities to evolutionary change. It is relatively easy to trace the grand evolutionary progression from single segment organisms, through multisegmented organisms in which the units are identical, to organisms with differentiated segments that carry wings, legs, and so forth. Each step—the increase in size permitted by stringing many segments together, and the introduction of versatility by making segments nonidentical—was a major evolutionary innovation. And it has become possible to describe the developmental events from egg to organism in many quite complex creatures. But the underlying mechanisms that guide the ordered assembly of cells and tissues still elude researchers.

Some, such as George Oster, of the University of California, Berkeley, look to local forces within and between cells to explain much of the assembly process. For instance, he has developed a computer model which, given just a small number of cell characteristics, describes the spontaneous and automatic transformation of layers of identical skin cells into an array of hair follicles. With slightly different properties, the cells self-assemble into feather-bearing skin.

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Others, such as Lewis Wolpert, of The Middlesex Hospital Medical School, London, favor assembly mechanisms in which cells "know" what to do through detecting their position in a developmental field. The concept of positional information is recognized as being extremely attractive, but hard data in its support are elusive. Some combination of local and distant information is likely to prove important in development.

In the search for fundamental laws of development and morphology, participants at the Dahlem meeting eagerly offered for consideration their experimental systems and made tentative claims for some degree of insight into the problem. Inevitably each presentation would be met by a chorus of, "But it's not like that in the leech/drosophila/chick limb/and so forth."

There is a bewildering diversity in biology that so far at least has dazzled researchers' eyes to the generalities they seek. As Brian Goodwin, a developmental biologist from the University of Sussex, England, put it: "There is so much detail before us that it is difficult to rise above it and develop levels of abstraction." Is there a rationality of form, something akin to the periodic table of the elements? asks Goodwin. Stuart Kauffman, of the Department of Biochemistry and Biophysics at the University of Pennsylvania, is convinced that "spatial and dynamic laws of organization" are there to be elucidated. "There have been few grand syntheses in biology beyond Darwin and Mendel's," he says. "Perhaps one will emerge here."

The Dahlem meeting contemplated the position of the embryo in the study of evolutionary mechanisms, to the virtual exclusion of other aspects of evolutionary theory. This was not meant to imply that development holds all the keys to understanding evolutionary change. Rather, the meeting was a rehabilitation process designed to push a neglected field of evolutionary biology closer to the center of the stage where it can join with other areas of study in shaping a fuller understanding of the origin of morphological novelties.

The message of the meeting was formulated by Gould. "Organisms are not pieces of putty, infinitely moldable by infinitesimal degrees in any direction, but are, rather, complex and resilient structures endowed with innumerable constraints and opportunities based upon inheritance and architecture (both molecular and morphological)." Gould points out that this is not a new insight, but it is one that requires restatement. "Organic integrity always received lip service," he says, "but in a subtle, yet pervasive way, the strict Darwinism of recent times has encouraged us to put this truth on the back shelf and to consider development primarily as a source of unconstrained, small, random variants that provide raw material only and make natural selection the sole directing source of evolution."

In summing up the meeting Gould borrowed from Francis Galton, Darwin's cousin, to leave participants with a visual image of the role of the organism in evolutionary change. Under strict Neo-Darwinism, the organism is perceived as a sphere that can be nudged in any direction by natural selection. The organism, in other words, exerts no influence over its evolutionary fate. Galton, by contrast, pictured the organism as a polyhedron, the facets of which represent internal constraints on the direction in which natural selection can push it. The facets, in the context of the Dahlem meeting, are to be seen as the consequences of physical possibilities and limitations imposed by developmental processes. "Natural selection may be the propelling force of change," concluded Gould, "but the organism participates in the process substantially by restricting the direction that change will take."

—Roger Lewin