

# *The Plausibility of Life*



*The*  
Plausibility  
*of* Life

*Resolving Darwin's Dilemma*

Marc W. Kirschner and John C. Gerhart

Illustrated by John Norton

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To Phyllis and Marianne



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## *Preface*

This book is about the origins of novelty in evolution. The brain, the eye, and the hand are all anatomical forms that exquisitely serve function. They seem to reveal design. How could they have arisen? The vast diversity of organisms, from bacteria to fungi to plants and animals, all are of different design. How did they originate? Nothing in the inanimate world resembles them. All are novel. And yet novelty implies the creation of something from nothing—it has always defied explanation. When Charles Darwin proposed his theory of evolution by variation and selection, explaining selection was his great achievement. He could not explain variation. This was Darwin's dilemma. He knew only that variation was indispensable as the raw material for selection to act on, and random with respect to the particular selection at work. Genetics provided important clues about the dependence of variation on genetic change and in particular about how change is inherited. What has eluded biologists is arguably the most critical: how can small, random genetic changes be converted into complex useful innovations? This is the central question of this book.

To understand novelty in evolution, we need to understand organisms down to their individual building blocks, down to the workings of their deepest components, for these are what undergo change. Insights into these components have come only in the past few years. A theory of novelty was impossible to devise until the end of the twentieth century; experimental evidence was incomplete on how the organism uses its cellular and molecular mechanisms to build the organism from the egg and to integrate the genetic information into functional pro-

cesses. Ignorance about novelty is at the heart of skepticism about evolution, and resolving its origins is necessary to complete our understanding of Darwin's theory.

The last 150 years have seen Darwin right and Darwin wrong; Darwin doubted, Darwin ignored; Darwin demonized, and Darwin idolized; but in the end we may have the true worth of his accomplishment. He came up with a single transcendent idea, variation and selection, and he demonstrated that idea through intense observation. This science is the simplest to appreciate; one might even say it is science at its purest. So convinced was Darwin of variation and selection, based on his empirical evidence, that he was willing to ignore or contrive mechanisms to explain it. The course for biologists has been ever more clear: to see if we can understand the mechanistic underpinnings of his transcendent idea.

Evolutionary biologists and paleontologists in their search for more evidence of selection and common descent have done their part, though their task is hardly complete. Geneticists, achieving spectacular success at the end of the twentieth century in solving the mechanism of heredity for all of life, have done their part. Still, they can do more with the modern tools at their disposal.

Developmental biologists, cell biologists, biochemists, and now genomicists have begun the arduous job connecting the bewildering amount of genetic change to the variation on which selection has acted. It is their insights that we report here. An understanding of the connection between the gene, on the one hand, and the anatomy, physiology, and behavior of the organism, on the other, can provide the explanation for novelty. Knowing the ease with which novelty can arise in turn helps us determine whether it is plausible that life is a product of evolutionary change.

In this book we propose a major new scientific theory: facilitated variation that deals with the means of producing useful variation. From an explanation of how such variation emerges comes an appreciation of the facility of evolutionary change. We present facilitated variation not only for the scientist, but also for the interested nonscientist who is ready to explore ideas at the forefront of biological theory. Recog-

nizing how difficult it is to speak to such a diverse audience, we owe both groups an explanation.

To the scientist, we ask forbearance that we have largely skirted the jargon and qualifying phrases emblematic of scientific writing. Yet many of our scientific colleagues who read drafts of this book strongly encouraged us to keep the language simple while making no concessions in the ideas. Even if we had tried to confine the message to professional biologists, we would have had problems. In which subfield would this book be understood? If it were addressed primarily to those who study molecular biology, would the ideas be familiar enough to those who study natural history? If addressed strictly to evolutionary biologists, our assumptions would disenfranchise most molecular biologists, who would find the questions peculiar and the examples exotic. We decided that a common, straightforward vocabulary was essential just to reach *scientists* as a group. To move beyond scientists to the lay public required further adjustments, but fewer than one might expect.

To the nonscientist, we would say that you have already revealed your deep interest in evolution and your appreciation that evolution affects your sense of self as a biological creature. In record numbers you have bought books, visited museums, traveled to exotic habitats, and attended courses and debates about evolutionary theory. Your intense demand for knowledge has been met by interpreters of science, often journalists, who have contributed to your understanding. But the barrier of ignorance of the molecular sciences has handicapped the lay public, as it has in fact handicapped many scientists as well. To be forced to occupy the worst seats in the theater for one of the most meaningful dramas in the history of human exploration seems tragic, especially if it is avoidable. The nineteenth-century discoveries in evolution filled museums with towering fossil skeletons of dinosaurs, which inspired children and adults alike. Zoos, arboretums, and animal programs on television have thrilled millions with the diversity of life on earth.

We are not sure that we can succeed as well in portraying the molecular and cellular understandings that complement and ultimately

explain this diversity. But we know from experience that a vivid real drama can be much more engaging than a paraphrased retelling. We have done what we could: reduced the jargon, emphasized the universal concepts, stayed true to the narrative of evolutionary history, and provided a glossary and ongoing explanations. What we have not done is dilute the ideas or turn arguments and demonstrations into uncorroborated assertions. We have tried to provide conveniences and aids, but there is no shortcut to understanding. We hope we have succeeded in both explicating a significant new theory in evolution and embracing a broad audience.

As an original, far-reaching recasting of evolutionary theory, our book has much to convey. We have high drama: the union of molecular, cellular, and developmental biology with evolutionary history; the story of how novelty was generated in evolution; the paradox of the conservation of fundamental mechanisms of the cell but the extraordinary diversity of organisms; a new cast of evolutionary mechanisms all based on trading constraint for deconstraint; and the completion of Darwin's theory with new evidence as to why his original idea of variation and selection works on the variation side as well as on the selection side. We hope that the magnitude of a retold story of creation will hold the interest of readers—specialists and generalists alike.

Ours is a journey from molecule to cell to organism to life's diversity. It is up to the reader to traverse the nearly four billion years of life embedded in our account. We have invoked the latest results from the molecular sciences, pressing chemistry, cell biology, developmental biology, biochemistry, and genetics into the service of evolutionary biology.

Understanding life is not a conquest, but a slow lesson in appreciation. Most of what we, the authors, have learned we learned from others; our own contributions are small enough that they rarely appear in this book. We, as scientists, have been and continue to be active participants in the process of discovering how the organism constructs itself. We continually confront the surprising admixture of conservation and diversity found in all organisms. Our lifelong pursuits of the conserved processes of life led us inexorably to the question of the

origin of novelty in evolution. Novelty by definition is always a surprise, but when the surprise is too great, it is completely implausible. The plausibility of life rests on the plausibility of generating novelty, and that in turn rests on mechanisms newly uncovered in biology.

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# *The Plausibility of Life*



## I N T R O D U C T I O N

## A Clock on the Heath

In 1802 the Reverend William Paley expressed his faith that life, full as it is of intricate design, must be the work of a Supreme and Intelligent Creator. In his now-famous metaphor, the minister wanders on the heath and stumbles across a brass watch. Plunged into thought, he asks how the watch came into being and reflects that his explanations are entirely different from those brought to mind when his boot hit a stone. The stone might have “lain there for-ever,” demanding no explanation. But the watch, with its carefully constructed wheels, teeth, springs, pointers, and oval glass face, each part perfectly suitable for the function of telling time, certainly must have been created by a designer of great skill. Even if the watch were broken or if we did not understand the workings of every part, our confidence in the existence of a designer would not be shaken. No one, Paley asserts, could believe that a purely blind and random process of trial and error could achieve the exquisite design of the “plainest” parts of the watch.<sup>1</sup>

Paley intended his homily to demonstrate the need for a Creator in life’s creation. “Every observation . . . concerning the watch may be repeated with strict propriety concerning the eye, concerning animals, concerning plants, indeed all the organized parts of the works of nature.” These works are far grander than a mere watch. As human beings are the only designers capable of creating a watch but are incapable of creating life itself, it is fair to deduce that a far greater Intelligent Creator of life must exist or must have existed.<sup>2</sup>

Paley compared the complexity of the watch, which he could understand, with the complexity of life, which in 1802 he could not, as a measure of their creators. However, such comparisons look different today. Where he would have seen an earthworm and a skylark each as a unique and complex design, we now see underlying similarities; they have the same system of heredity, the same genetic code, the same cellular makeup, the same subcellular components, largely the same metabolism, and many of the same processes of embryonic development. Paley was on a firm footing in distinguishing the stone and the watch, but not in comparing the watch and the skylark, the worm, or the eye. He had every reason to see each as an independent act of creation. All he saw in common was their complexity, not the nature of the complexity, and it is that nature that tips the balance between acceptance of evolution and the alternative deism that Paley chose.

Fifty years later Charles Darwin guessed right. In the 1850s only a little more was known about the constituents of living things, such as the existence and continuity of cells. Darwin used his imagination to replace a supreme designer with a process of evolution by natural causes. He theorized that in a population of organisms, minuscule heritable variations of design arise at random in each generation, and some rare variant members are by chance more fit to reproduce under the selective conditions, a process known as survival of the fittest. As the other designs are rejected, the altered design of the survivors is perpetuated. Evolutionary adaptation is improved design for life.

Here and throughout this book we use the word *design* to mean a structure as it is related to function, not necessarily implying either a human or a divine designer; it is a commonly used term in biology. With time, according to Darwin, large novelties of design accrued from sequentially selected small novelties. As the process was repeated (and as the lineage of descendants repeatedly branched), a single primordial cell gave rise to all life forms on earth, including human beings. It might take a long time with many individuals dying in the line of service, but better adaptations would eventually result from the modification of previous adaptations, toward the same or new purposes.<sup>3</sup>

Neither Paley nor Darwin could directly observe the events of creation. Both Divine Creation and evolution by variation and selection were hypotheses. In the 150 years since Darwin, natural selection has been amply demonstrated by biologists who have trolled the ocean and scoured forests and barren lands to identify new species and unearth fossils. But does natural selection fully explain the diverse complexity of life on earth? Darwin himself waffled about the relative importance of variation and selection for the creation of novelty. Was variation rare and channeled in specific favorable directions? Or was variation so common that any trait would be likely to occur at some frequency?

Initially, Darwin thought that variation was common and therefore selection was for him the only creative force in evolution. Variation was required, but selection molded the chaotic profusion of small changes into the exquisite design of organisms. In this light, variation seemed less important than selection. In later life, though, Darwin gave variation a larger role in evolution, though not a freely creative one. He accepted the view that the environment directly instructs the organism how to vary, and he proposed a mechanism for inheriting those changes. He retreated from the notion that variation was random with respect to environmental conditions. The more important he made the environment in determining the kind of variation, the less was its importance as a selective and creative agent.

This ad hoc theory was at first proclaimed as Darwin's second monumental achievement, after the theory of evolution. Yet it was completely wrong. The intuition that served Darwin the naturalist so well in the *Origin of Species* failed him when he tried to understand cellular mechanisms and inheritance. In the years after Darwin, his original ideas were restored. Variation was again seen as random and providing the essential material on which selection could act. Variation was recognized as the source of novelty; the environment could not produce anything new through the selective process.

The notion of random variation as the sole generative force behind novelty raised other problems as well. Darwin worried about complex organs such as the eye, where multiple independent events must have

preceded the appearance of the first working eye. An eye requires a lens to form images, and a retina of photoreceptors to receive them, and long nerves to communicate signals from the retina to special parts of the brain. Would the intermediate eye be any more functional than a partially assembled watch? If not, how were intermediates maintained so that slowly over time new parts could be added until a selectable function was achieved? Though anticipation and planning to meet multiple demands are common tasks for intelligent beings, they are hard to achieve by random variation and selection.

Thus, the problem of novelty's origin in evolution becomes, How could the eye be created in the first place, or the brain, or wing, or lungs, or limbs? Could they have been plausibly assembled, small piece by small piece, each presupposing a selective advantage? It is this feature of Darwin's theory, the uncertain accounting for novelty, that creationists seize on; meanwhile, evolutionary biologists assert that variation must be sufficient, though they lack a general explanation for the origin of complex novel structures. Answers to these questions affect the plausibility of life's arising by way of evolution.

Science in Darwin's time could not provide satisfactory answers about the nature of variation. Darwin simply chose a catechism different from Paley's on which to base his interpretation of creation, namely, that heritable variation is generated by some means, and selection then sifts the variants for those most reproductively fit. It was an interpretation that we now recognize as modern, completely based on natural events and laws, but one that better describes improvements than it does origins. It gives us no idea of how fast or how readily things could change, or whether evolution is channeled in certain directions by the kind of variation that an organism can produce. To this day, the explanation for novelty has remained hidden within the organism. Paley went straight to an ultimate cause: a Creator about whose means of creation we can know nothing more.

For a while in the twentieth century, the concept of the gene and mutation seemed to provide the answer to evolutionary change; namely, if a gene is altered by mutation, the descendants inherit the change, and depending on the nature of that particular change, the descendant

would differ in some trait of its anatomy, physiology, or behavior. It now appears that the concept provided only a partial answer, that genetic change is required for heritable variation. Genetics tells us a great deal about the inheritance of change and the spread of the required gene in a population of reproducing animals when the trait is under selection. Still, it does not tell us much about how genetic change causes complex changes in organisms. Only in the last few decades have such cellular and developmental mechanisms been identified. These mechanisms speak most directly to the question of the origins of novelty.

To show the vantage point of our times, let us imagine a twenty-first-century descendant of Paley, more than two hundred years removed from the author of the homily on the watch, wandering the heath and still wondering about the origin of plants and animals. She brings with her an education in modern biology, including genetics, cell and developmental biology, and evolution. She does not have the good fortune to stumble upon a brass watch (they are getting harder and harder to find), but instead muses philosophically about life itself, the heather, the flies on the heather, or the mouse underfoot.

Like her famous ancestor, she is fascinated by measuring time. She notices that plants extend their stems below the flower just before sunrise. She notices on a longer time scale that some plants flower early in the season when days are short, whereas others flower at the peak of the summer when days are long. She notices in herself that she has a daily cycle of sleep and restlessness and that she has suffered recently from jet lag, thereby raising her personal awareness of her endogenous clock. She realizes that most kinds of plants and animals, even fungi and bacteria, have such clocks; being experimentally inclined, she might have placed a mouse in total darkness and found that its 24-hour cycle of sleep and waking continues for many days without cues of light. As an avid student of time, she might know that accurate time pieces were once difficult to make, especially ones that kept time when jarred or heated or cooled. By comparison, biological clocks function accurately in animals while they run, jump, and swim through life, on hot or cold days.

Also, Paley's modern descendant is understandably impressed to know that virtually every cell in our body, each weighing less than a billionth of an ounce, contains an accurate temperature-compensated chronometer, whereas the first accurate chronometer in human history, circa 1736, weighed 72 pounds (33 kg).<sup>4</sup>

By now the younger Paley, seeing the performance of biological clocks, might be even more tempted than her ancestor to invoke the Creator. But living in the twenty-first century, and with her background in modern biology, she can examine for herself the workings of the biological clock in a way her forebearer could not. She avails herself of the electron microscope, the various tools of molecular biology, the geneticists' collections of mutant animals and plants defective in various aspects of their timing, the sequences of the genomes of numerous animals and plants, and the computerized databases available worldwide.

On her worktable she quickly assembles the clocks of human beings, mice, flies, fungi, and plants. These are known as circadian clocks from the Latin *circa*, approximately, and *dies*, day. How are they constructed? Are they fashioned out of special materials, unknowable to humans? Do they work by means beyond her comprehension? Is each a unique event of creation, different from all other circadian clocks? Does their design offer clues about the designer? Does each clock so far exceed human imagination in its uniqueness, complexity, and perfection that it could never have arisen by the gradual modification of parts affected randomly by mutation and then selected? Or might there be a surprise here, an unexpected glimpse of a plausible creation by natural means?

Man-made clocks, like biological clocks, run by converting a continuous process into a repetitive process. Although they share this common principle, their inner workings are distinctly different. The Chinese water clock of the eleventh century was based on the periodic filling and emptying of vessels attached to the rim of a wheel, into which water flowed at a constant rate. The pendulum of a grandfather clock is kept in motion by weak nudges from falling weights. The oscillating escapement of a brass watch is driven by an uncoiling spring.

The quartz watch uses an electrical current to cause a crystal to vibrate at a characteristic frequency. Though all convert a continuous process into a periodic one, they share few components of their internal time-keeping mechanism.<sup>5</sup>

Unlike man-made clocks, circadian clocks from disparate sources share many features of design and materials. Turning to the components of the clock, the modern Paley would find that most are used elsewhere in the organism in other roles having nothing to do with clocks and are far from being unique. They are all made of proteins and most of these proteins resemble other kinds of proteins. Furthermore, when she compares the components of the circadian clock in the fruit fly with those in the mouse, she finds that many of them are the same, but some are used differently in the two circuits. The interactions of the different clock components are not strictly conserved, but they can still generate periodic behavior. It is as if the genes and encoded proteins act as individual transistors suitable for wiring in different ways in the integrated circuit timers of a mouse or of a fly.

Thus, the circadian clock is not like a brass watch, where each component is made for just one purpose. The human-engineered clocks use different techniques to achieve the same result; the circadian clocks use a common set of techniques. Novelty in human clocks requires independent acts of invention. Novelty in biological clocks seems more suited to iterative modification from a common origin.

No matter where she turned, whether to the nervous system, the embryo, or the behavior of cells, young Paley would find examples of multiple and varied reuse of the same components. The properties of components facilitate their reuse, new use, and rampant invention. She would not find a boundless variety of completely different objects performing complicated activities, of the sort that demand a supreme Intelligent Designer to explain their origin. She would not even be tempted to follow the trail in that direction, so enthralled would she be by what organisms have managed to do with the limited cellular components at hand.

Indeed, a similar moment of introspection arose for many biolo-

gists in the year 2000, with the publication of the “rough draft” sequence of the entire human genome. It was realized that we possess 22,500 genes, only six times the number possessed by a bacterial cell, the simplest of all known free-living organisms. How could human complexity be achieved with so few genes? Then, in the next few years, the genomes of bacteria, fungi, plants, fish, and mice were sequenced and compared, and it turned out that many genes are similar across these disparate species, apparently conserved from remote ancestors. How can their differences of anatomy, physiology, and behavior be explained when many of their genes are so similar?

The answer, the young Paley infers, lies in the multiple use of versatile conserved components. It is not the clock in particular that is so remarkable, but the multifunctioning protein components and their forms of regulation that allow them to be easily connected in many ways toward various ends. The living organism is certainly more complex than the brass watch in terms of the number of components and the variety of their interactions, but it is complex in unusual ways appropriate for versatility and modification rather than for dedicated single use. In the end, the young Paley would conclude that biological clocks do not imply a human creator or a divine Creator, but something else—call it a creation of biological novelty through natural causes.

Our story of the two wanderers on the heath brings us to the heart of this book. We begin where the younger Paley left off, at the question of the origin of complex life. We bring to the inquiry the understanding of many processes of living organisms, not just clocks, gained in the past few decades by a worldwide community of biologists. It is an understanding obtained at the level of the chemical components of organisms, their activities, and their interactions, with glimpses of their evolution.

The cardinal issue in evolution is the origin of complex and heritable variation from a limited reservoir of components. Although selection has preoccupied evolutionary biologists, the study of the origin of variation and novelty has idled. Is the organism’s capacity to generate heritable variation great enough to supply the succession of variants needed for natural selection to bring forth a circadian clock, or—more

challenging—a human being from a single-celled ancestor, all within the time span of the earth? Heritable variation requires mutational change of the genome, but that is only the start of the story.

What else is required to get an adequate frequency of selectable variants? Mutation only changes what already exists. It does not create new anatomy, physiology, and behavior from nothing, so we need to know how readily one structure can be transmuted into another, particularly when we consider structures of intricate design and interdependent activities. With an understanding of how random genetic change is converted into useful innovation, a theory of novelty can be devised. Darwin's general theory of evolution can then be established at the most fundamental level.

## O N E

# The Sources of Variation

Physical scientists in the nineteenth and early twentieth centuries had astounding success in formulating very general yet predictive theories in thermodynamics, electricity and magnetism, and atomic structure. Biology sought a similar level of generalization and had signal success in the cell theory, the germ theory of disease, metabolism, and heredity. Darwin's theory of evolution was perhaps the most ambitious effort to understand the living world, but unlike the others it was historically based and hard to test experimentally. Even to be comprehensible, it required an accumulation of knowledge from natural history, genetics, and paleontology. Biology differed from physics in that its most obvious characteristics are complexity and diversity; therefore the origin of that complexity and diversity would remain at the center of biological concerns. At the end of the nineteenth century, evolution was an unfinished, still controversial theory. An explanation of the origin of variation was one of the big gaps. The incompleteness of the theory was a problem for all of biology; biologists would continually return to it to add their perspectives.

## The Three Pillars of Darwin's Theory of Evolution

Darwin's all-encompassing theory of evolution was based on three major supports: a theory of natural selection, a theory of heredity, and a theory of the generation of variation in the organism. In Darwin's

view, rephrased in modern terms, organisms within populations vary genetically and consequently differ in traits that affect their capacity to contribute to the next generation. In competition with one another and facing other pressures in the environment, the most fit organisms flourish and the less fit fail to contribute progeny to the next generation. This process selects a better-adapted subset of the population that carries within it a different set of genes and therefore manifests a different set of properties. The population is said to have evolved under selection, making use of its genetic variation.

From the start, it was natural selection or the struggle for existence that required the smallest leap of imagination. The selective death of “weaker” individuals is universally appreciated; Darwin employed his encyclopedic knowledge of biology and his persuasive logic to draw out the consequences in a robust argument that has lasted to the present day. Artificial selection was familiar to all plant and animal breeders, and the extrapolation over long periods to a “natural selection” was plausible. Still, some critics denied its effectiveness as the only mechanism for producing very large anatomical changes, such as had occurred in the evolution of complex animals from single cells or of human beings from animals.

By contrast, heredity was not properly understood in Darwin’s time. Today it is largely a solved problem. With the deciphering of the structure of DNA in 1953 came a sophisticated understanding of genetic variation and its inheritance. Genetic variation is due to mutation (a change in sequence of the chemical letters that make up the DNA code—A, T, G, and C), to recombination (the splicing together of DNA segments from different chromosomes to form hybrid chromosomes), and to assortment of chromosomes during egg and sperm formation. All of these factors, separately and together, change the DNA sequences of an offspring, and these changes are reliably inherited.

For some biologists, basking in the grand accomplishments of genetic theory, understanding that DNA changes its sequence randomly at very low frequency (a few positions in a billion bases of sequence, each round of replication) and that DNA is otherwise copied

at high fidelity at each cell division, meant that a comprehensive theory of heredity could join a well-developed theory of selection to complete Darwin's transformative idea. For others, a major weakness remained, casting all else in doubt. Their unanswered question was whether random change and shuffling of DNA could ever lead to highly complex and wonderfully adaptive innovations in anatomy and physiology such as the eye, the brain, or even the peacock's tail. The Reverend Mr. Paley's skepticism, shared by some scientists as well as by many laypeople, might not be satisfied by a theory of evolution that rested solely on a theory of selection and a theory of the inheritance of random DNA changes.

In evolution, selection always acts on variation of the *phenotype*, which includes all the observable and functional features of the organism. This is a favorite word of evolutionary biologists, as in "phenotypic variation" or "phenotypic change." Selection does not directly act on the DNA sequence (also called the *genotype*). It acts on the genotype only indirectly through the phenotype, most details of which depend on the genotype. The organism's size, its speed, its visual acuity, its resistance to disease, its behavioral responses—all are part of the phenotype. DNA itself has none of these activities. Since the phenotype faces selection but the genotype is what is inherited to produce the phenotype, it is crucial to understand the processes that connect the two.

The question unanswered by the two well-established pillars of evolutionary theory (selection and heredity) is whether, given the rate and nature of changes in the DNA, *enough of the right kind* of phenotypic variation will occur to allow selection to do its work, powering complex evolutionary change. If the organism were a machine, like Paley's watch, we would expect that random alterations either would have little effect or would lead to catastrophic failure. We would not expect random change to cause the clock to run more accurately or to develop new features, such as a snooze alarm! But is an organism like a watch, or is it made in a fundamentally different way? The question was unanswerable until the very end of the twentieth century. No clues existed in Paley's or Darwin's time. In later chapters we will argue that

understanding the organization, growth, and development of the organism is essential to complete Darwin's theory.

There are limits on what selection can accomplish. We must remember that it merely acts as a sieve, preserving some variants and rejecting others; it does not create variation. If genetic change were random, what could ensure that enough favorable phenotypic variation had taken place for selection to have produced the exquisite adaptations and variety we see on the earth today? At various times, biologists thought that genetic change must be directed in some way to produce enough of the appropriate kinds of phenotypic variation. If selection were presented with a preselected subset of variants, that might greatly facilitate evolutionary change. Or if the organism generated just the right variants, selection might not be needed at all. Thus, the efficacy of selection would depend on the nature of phenotypic variation, which in turn depends on the amount and type of genetic variation and on the mysterious process by which phenotype emerges from genotype.

Is genetic variation purely random, or is it in fact biased to *facilitate* evolutionary change? By *facilitated genetic variation*, we mean genetic variation that would be (1) biased to be viable (only nonlethal variation is heritable, the rest from the point of view of evolution is useless); (2) biased to give functional outcomes; and (3) biased to be relevant to the environmental conditions. A few biologists tried to invent theories about how the environment might alter the parents' genetic endowment to their offspring. As attractive as it would be to discover a process for loading the genetic dice, thereby improving the rate and course of evolution, there is in fact no evidence for facilitated *genetic* variation and there is conclusive evidence that it does not exist. The process of evolution receives no help from this quarter, and within our modern understanding of the organism it would be hard to imagine how such a process could work.

By 1940 it was clear that genetic variation was random and unlinked to environmental conditions. Stripped of these concerns, evolutionary biologists formulated a theory based on purely random (unfacilitated) genetic variation and on selection. This was the Modern Synthesis, the current consensus model of evolution. The theory,

however, was codified before the dawning of modern molecular biology, cell biology, and developmental biology (a more modern term for embryology, which includes the study of stages other than embryos). Evolutionary biologists could not say much, even in theoretical terms, about how the organism constructs itself, its phenotype, from its genetic instructions, its genotype. The Modern Synthesis is a valuable model but an incomplete one. It lacks the third pillar required of a general theory of evolution, a pillar needed to explain the feasibility of evolutionary change.

This third pillar is a theory of how genetic variation is used in the generation of heritable phenotypic variation. It is a theory of how the inherited genetic material along with the environment constructs the individual organism in each generation, from the egg to the adult and on to the next generation. The organism's anatomy, physiology, and behavior are only remotely connected to the DNA sequence through all the complex processes of growth, development, and metabolism, though they depend on it. A change in the DNA sequence is therefore only indirectly correlated with a change in the anatomy and physiology of the organism.

Currently, our understanding of this connection is not sufficient for us to predict the phenotypic consequence of most genetic changes. We can identify genes that predispose a person to cancer, but we cannot draw a perfect correlation between gene and disease. Given the remote connection between the DNA and the phenotype, we have no way of knowing how often random DNA modification can produce useful outcomes for selection. Without an understanding of how DNA changes are interpreted, we cannot know how much selection molds evolution, or how much the initial variation biases the outcome.

It is not enough to know that changes in DNA can in some unknown way cause a change in phenotype; we need to know at least in outline how phenotypes respond to particular changes in DNA. It is this third pillar, an understanding of the organism's response to genetic change, that is our subject here and the resolution to Darwin's dilemma. The overall outline of this very modern story is so new that it is only dimly perceived, and its implications for evolution have been

only partially discerned. Before we consider the role of the organism in responding to genetic change, we need to understand whether there is an environmental bias in how the DNA changes. Then we can add the final pillar to Darwin's basic outline and construct a more plausible and more complete theory of evolution.

### How Random is Variation?

Among the first ideas of how variation might be generated and inherited were those of Jean-Baptiste Lamarck (1744–1829), a French biologist who was among a group of scientists believing, as Aristotle had, that organisms have changed over time rather than having been fixed since the moment of their creation. Like Paley and many others, Lamarck had marveled at how well living organisms are adapted to their environment. He looked for a means to match these adaptations to environmental conditions during the course of evolution. In his *Philosophie zoologique*, published in 1809 (the year of Darwin's birth), Lamarck proposed two laws. The first restates a common observation about use and disuse: "In every animal . . . more frequent and sustained use of an organ strengthens that organ . . . while the constant disuse of an organ imperceptibly weakens it . . . and ends in its disappearance."<sup>1</sup>

His second law is novel and extends the process of adaptation to the generation of heritable change: "Everything that nature has caused individuals to acquire or lose by the influence of the circumstances, it preserves by heredity and passes on to the new individuals descended from it."<sup>2</sup>

In Lamarck's view, an animal's perception of and response to stressful circumstances is based on physiological and behavioral needs, not emotional and conscious desires. He focused on the influence of behavior on evolution as a stimulus for evolutionary change.

Lamarck's best known example is the giraffe. He supposed that the pre-giraffe, in meeting its need to feed, stretched its neck and forelegs. The human neck can adapt physiologically, as illustrated in Figure 1. In Lamarck's view, an acquired physiological adaptation of a

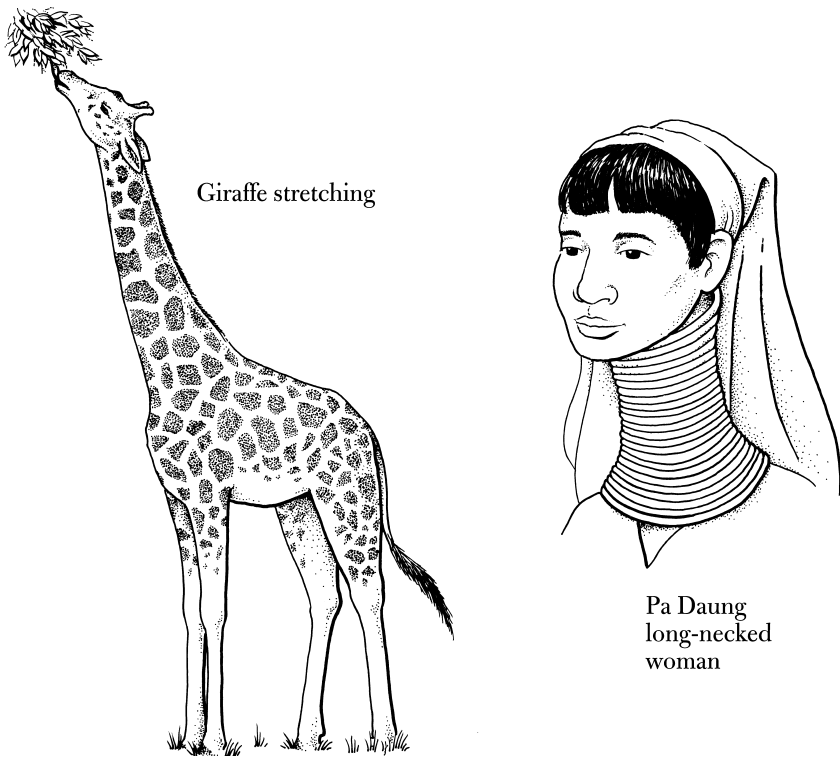


Figure 1 The elastic neck and Lamarck's theory of evolution. *Left*, the giraffe stretches its neck for food. *Right*, a woman of Pa Daung, Myanmar, with neck rings. In neither case is increased neck length, gained by stretching, transmitted genetically to the next generation.

longer neck and forelegs in the giraffe (Figure 1) was passed to the offspring who continued stretching until the long-necked, long-legged giraffe of many generations later did not need to stretch any farther. Presumably, many members of the pre-giraffe population could change as a group, not just as a rare giraffe variant.

Another example for Lamarck was the pre-ibis or pre-crane, which realized the need to keep its feathers dry, stretched its legs to rise above the water, then lengthened its bill to reach the fish in the water, and stretched its toes to create large webbed feet—accomplishing all this over many generations. Presumably, many members of the population changed together. It was a perfect gradualist idea. Throughout

this transformation, the behavioral need drove the anatomy. "It is not the shape either of the body or its parts which gives rise to the habits of animals and their mode of life; but it is, on the contrary, the habits, mode of life and all the other influences of the environment which have in the course of time built up the shape of the body and of the parts of animals."<sup>3</sup>

So self-evident and appealing seemed the view of facilitated heritable change, or more commonly called *inheritance of acquired characteristics*, that Darwin himself could not escape using it. Even though he proposed in his 1859 *Origin of Species* that change was random and selected later, he felt his hypothesis incomplete until he could identify how heritable variation arises in the first place. He increasingly retreated to Lamarck's view that different circumstances evoke different responses in organisms, which somehow pass to the next generation; that is, the environment facilitates or induces the kinds of adaptations appropriate to the environment. In 1868 Darwin published his two-volume work on *The Variation of Animals and Plants under Domestication*, presenting his model of the inheritance of acquired characteristics. In justifying his surrender to an overtly Lamarckian theory, he wrote:

How again can we explain the inherited effects of the use or disuse of particular organs? The domestic duck flies less and walks more than the wild duck, and its limb bones have become diminished and increased in a corresponding manner in comparison to those of the wild duck. A horse is trained to certain paces, and the colt inherits similar consensual movements . . . How can the use or disuse of a particular limb or part of the brain affect a small aggregate of reproductive cells, seated in a distant part of the body, in such a manner that the being developed from these cells inherits the characteristics of one or both of the parents? Even an imperfect answer to this question would be satisfactory.<sup>4</sup>

Darwin "imperfect answer" was pangenesis, his theory of inheritance. In pangenesis, the parent's entire body influences the next

generation by influencing the germ cells (egg and sperm). In this way, novelty is more efficiently generated in the offspring. Darwin suggested that minute elemental particles—we would now call them informational particles—are given off by all cells of the body and circulate through the individual. The more a cell is used, the more particles it gives off. Eventually the particles concentrate in the germ cells, their numbers reflecting the adult's lifetime of experience and physiological adaptation to the environment. Once passing from the germ cells into the embryo, they affect the development of the offspring by emphasizing those aspects that had been most called upon in the previous generation. The representation of these elemental particles in the germ cells seemed to reflect actual physiological usage rather than perceived needs, so the idea was not as need driven as Lamarck's. Variation was not random, but directed by circumstances, and was carried into the offspring by the sperm or the egg.

Darwin's was a self-consistent theory for the generation of variation, based solely on the inheritance of acquired characteristics. Pangenesis was an immediate success, but its author had created a dilemma for himself. The more successfully an animal generates appropriate variation in response to the local environment, the less the local environment needs to act through natural selection, preserving one variant from a multitude of others. In the extreme, there would be no need for natural selection at all; the organism would merely change as dictated by the environment. Darwin seemed to conflate variation and selection, and this fusion demanded further explanation.

In retrospect, it was difficult for thinkers of the time to break from the notion of directed heritable variation (although Darwin himself had done so earlier in his first theory) and to accept the possibility of pure random variation. It was hard to imagine that random events on their own could create a kind of novelty adaptive to the selective conditions. By direct reference to the ultimate physiological target, pangenesis or any of the other non-Mendelian ideas of directed inheritance avoided the need for stepping-stones to the new phenotype. Attractive as these ideas were, they were completely without foundation.

## The Disproof of Facilitated Genetic Variation

Subsequent years of experimentation brought no support for the direct inheritance of physiological adaptations of the organism to the environment. On the contrary, substantial evidence accumulated for the view that pangenesis did not exist.

The first steps in distinguishing physiological adaptation (the subject of Lamarck's first postulate) from heritable variation (the subject of his second postulate) came in 1895 from August Weismann. He showed that it was extremely unlikely that the sperm and egg could receive any information from the environment.

Weismann asked a simple anatomical question, "Where in the developing embryo are the specific cells that later become the eggs and sperm in the adult?" Studying jellyfish, he found that germ cells of the adult arose from precursor cells that were clearly segregated from other cells. Only after the jellyfish developed to the adult stage did these cells migrate into the gonad from their isolated site.

The initial segregation of the germ cells has been confirmed by modern studies of many kinds of animals including insects and all vertebrates, as illustrated in Figure 2. The cells of the body, called somatic cells (from *soma*, the Greek word for body), are the ones that experience and respond to stresses of the environment; they make no contribution to the distant germ cells, which are the only cells able to contribute to the next generation. The germ cells, by comparison, are shielded and removed from environmental influences. Weismann considered Darwin's pangenesis theory to be completely *ad hoc*. He criticized it delicately: "His [Darwin's] assumptions do not, properly speaking, explain the phenomena. They are to a certain extent a mere paraphrase of the facts . . . based on speculative assumptions."<sup>5</sup>

Weismann's idea of the soma-germ-line distinction has stood the test of time. No influence from the external environment that impinges solely on the somatic cells can modify the hereditary material for the next generation, which is exclusively within cells of the germ line. Conversely, since germ cells do not perform physiological functions in the organism and hence cannot be directly selected upon by the ex-

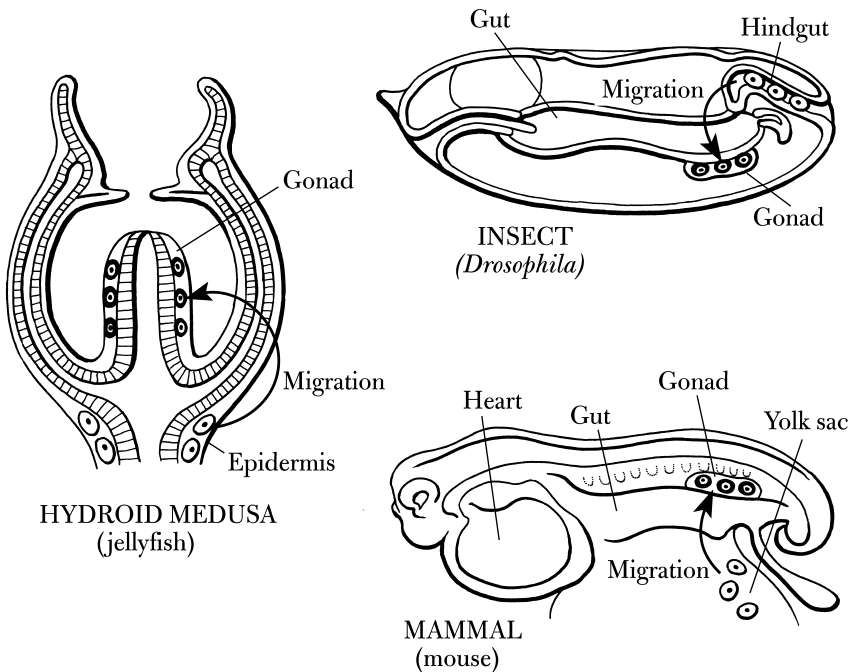


Figure 2 The separation of the germ line and the body. Germ cells are initially separate from cells in the developing embryo; later they migrate into the gonads of the embryo and differentiate into eggs and sperm. *Left*, the jellyfish example discovered by August Weismann. *Upper right*, an insect. *Lower right*, a mammal.

ternal environment, nothing in the environment can influence them to transmit specific traits preferentially to the next generation. The germ cells are coselected as mute passengers, in the vehicle of an organism made up of somatic cells with the same genetic makeup as they have. The only selection that can take place is the survival and reproductive success of the entire individual derived from a fertilized egg. A principal biological advantage for sequestering germ cells from the soma may be to assure that they reflect only the success of the whole individual, instead of the success of any selfish somatic lineage of cells within the individual that could most influence them. Weismann added to Darwinian evolution the cell-biological evidence that nullified the concept of the inheritance of acquired characteristics.

*Looking for Macromutations*

Although Weismann produced strong arguments against facilitated genetic change, they did not quite sound the death knell for that idea. Variation and heredity were certainly the heart of evolution, and an understanding of the nature of variation in clear chemical and physical terms would be necessary before one could claim that the facilitation of variation could not occur by biasing genetic change. Hence, understanding variation and settling the issue of whether it was random or not was extremely important. As we shall see, the problem of genetic transmission became such a compelling problem in its own right that it quickly eclipsed the problem of evolution.

Before the twentieth century's rediscovery of Gregor Mendel's work, the importance but not the nature of variation was evident. The future geneticist William Bateson wrote in 1894: "Variation, whatever may be its cause, . . . is the essential phenomenon of Evolution. Variation, in fact is Evolution. The readiest way then, of solving the problem of Evolution is to study the facts of Variation." He scoured the world for freaks of nature—human feet with eight toes, turtles with two heads, horses with an apparent atavistic formation of multiple metacarpal bones, insects with all limbs duplicated—enough to convince himself that variant individuals occur in populations at detectable levels.<sup>6</sup>

Bateson was famous for his study of "homeotic" variation (meaning a change into the likeness of something else), which resulted in a class of variants with serial repetitions of anatomical features such as extra digits or wings. The common appearance of well-proportioned duplicated appendages might have been a clue that variation was distinctly nonrandom. Later, homeotic variation experimentally induced by mutation would provide a critical insight into how the organism develops. These insights, in turn, provided a key to our theory of facilitated variation.

However, in 1894 Bateson must have been very disappointed. In his nearly six-hundred-page book entitled *Materials for the Study of Variation*, he could provide no mechanism for the origin of homeosis

or any other kind of variation, except to say that embryonic development had been altered.

Although the study of phenotypic variation was proving to be a dead end at the turn of the twentieth century, the study of heredity was bursting with opportunity. The second pillar of Darwin's theory was about to be triumphantly established, but ignorance of the mechanism of phenotypic variation has lingered until the present. At first an understanding of genetic variation, coupled with a theory of selection, seemed all-powerful; but the problem that was actually solved was how information was transmitted from one generation to the next, not how novelty originated.

The modern story of genetics began in 1900 with the rediscovery of Gregor Mendel's 1866 paper "Experiments in Plant Hybridization." By then, many biologists and naturalists were breeding plants systematically and observing the distribution of the phenotypic differences to the offspring. Thus, Mendel's paper could be resurrected and appreciated. Variation in organisms could be divided, as we have said, into two categories: genetic change and phenotypic change. Genetic change occurred in the abstract but increasingly manipulatable realm of the organism's genotype (now defined as the information coded in the genome, the DNA sequence of the four chemical letters A, T, G, and C), whereas phenotypic change took place in the observable but still baffling realm of the organism's anatomy, physiology, development, and behavior—some of which was heritable and some of which was dictated by the environment.

After the successful sequencing of many genomes of bacteria, fungi, plants, and animals, information about the genotype is in principle both precise and complete. Plainly stated, the genotype is the organism's DNA sequence. There is no ambiguity. In the early days of genetics, the genotype could only be inferred from mating experiments, using some element of the phenotype as an indicator of the state of the genotype. (Mendel used color and texture of peas, for example.) The use of the phenotype to signify the genotype was an unavoidable but indirect method. Today the genotype can simply be read out as a

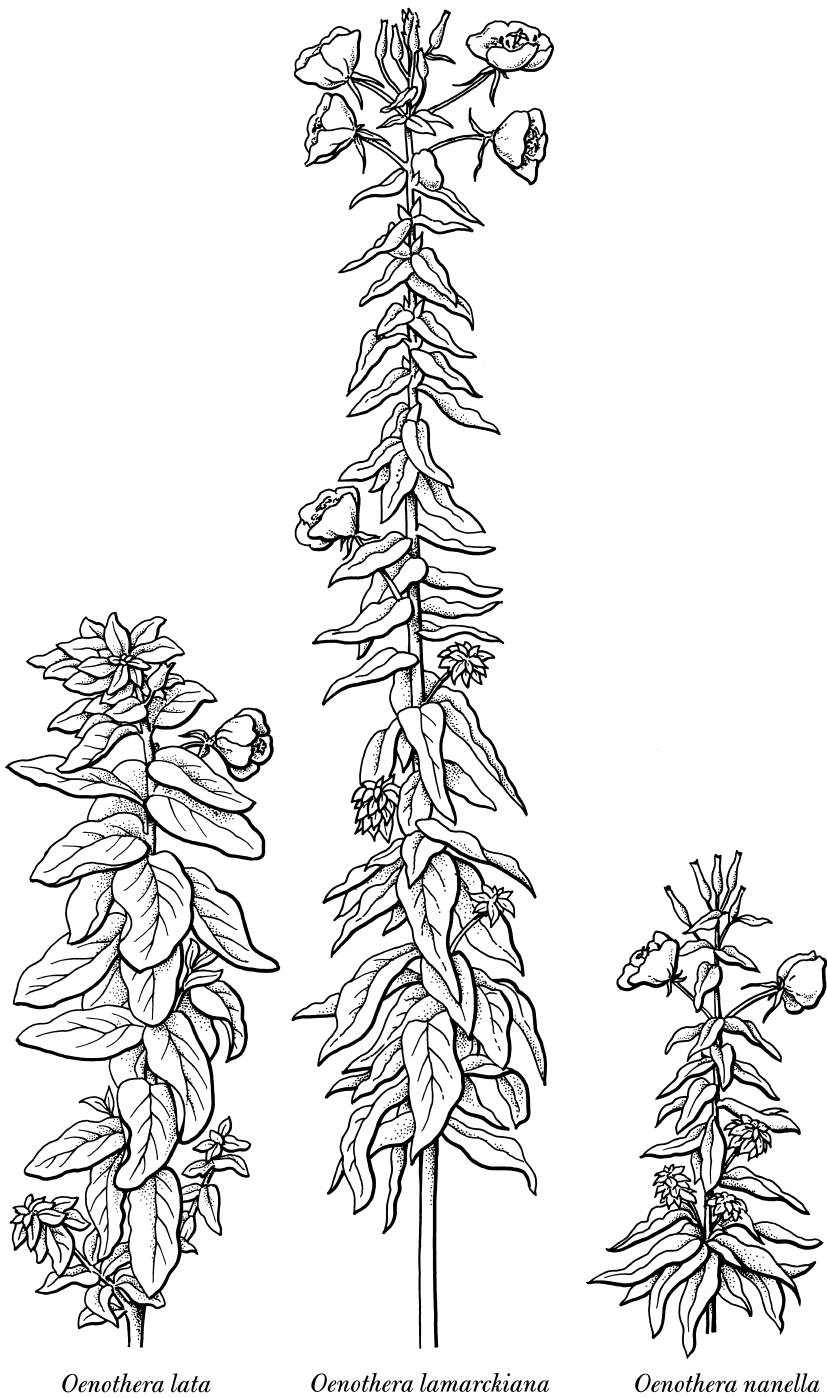
sequence from the DNA, over a billion letters long for many animals, much like a computer program.

The phenotype is a much more daunting matter. To understand it means to understand all the events of embryonic development, growth, maturation, and experience of the organism. It is everything that contributes to what an organism is, what it looks like, how it functions, and how it behaves. It is easy to see why, before Mendel's work was rediscovered, phenotypic variation was the major question for people interested in evolution; it was what was observable and what natural selection directly acted upon. After 1900, however, understanding of genotypic variation and the transmission of genes became major concerns for geneticists. Phenotypic variation was put aside. Bateson and others turned to the new field of genetics (he invented the word) as a full-time pursuit, with increasingly less regard for the problems of evolution.

Understanding evolution had been very much in the minds of the early geneticists; it was often the question that impelled them to enter science. Thomas Hunt Morgan, who later became indisputably the greatest American geneticist, visited the garden of Hugo de Vries in Holland in 1900 to examine for himself the first evidence for *macromutation*, the supposed evolutionary transformation of one species into another in a single mutational event.

What Morgan would have seen in de Vries's garden was an assortment of aberrant evening primroses, collected by de Vries, that had arisen occasionally and spontaneously in neighboring fields. The aberrations were drastic, creating what seemed like new species within a generation or two. Some plants had red veins on the leaves instead of colorless veins, some were larger or smaller, some possessed smoother or longer leaves, and some had modified flowers, as illustrated in Figure 3.<sup>7</sup>

Macromutation seemed to solve many of the problems of heredity and evolution in Darwin's theory of gradual change. Small changes would not need to accumulate over many generations, with each generation running a very real risk of being diluted by interbreeding with



*Oenothera lata*

*Oenothera lamarckiana*

*Oenothera nanella*

Figure 3 Macromutations in the evening primrose, *Oenothera*. Center, the stock cultivated by Hugo de Vries. Left and right, two short “species” that suddenly mutated from the stock.

normal individuals. The mutant plants, because of their large differences, might prevent interbreeding; since they arose commonly enough, those of similar kind could isolate themselves into new breeding associations. The sudden appearance of a new species could explain the gaps in the fossil record.

As a convert to the experimental method, Morgan ultimately sought ways to test de Vries's theory in other organisms. He would fail completely. We now know that the macromutation in the evening primrose is not a general phenomenon but is caused by a rare and peculiar genetic mechanism of that hybrid species. Macromutation in the evening primrose was a complete dead end for the study of evolution.

Morgan chose the fruit fly as a subject to test the generality of de Vries's observations. He propagated fruit flies in the dark for many generations to see if their eyes diminished, perhaps in a single stroke, like the macromutations in the evening primrose. There was no loss of eye structures even after 49 generations in the dark, therefore no evidence for hereditary loss through disuse either rapid or slow. Morgan generated many small heritable changes of phenotype, which were viable and fertile, but found no massive transformations like the evening primrose macromutations.

Then, one day in 1910, Morgan found a peculiar mutant fly that changed the course of biology. It was not a dramatic mutation, but was unusual. It marked Morgan's transition from an experimental evolutionary biologist to an experimental geneticist. Concurrently, interest in evolution was generally declining among many mainstream biologists.<sup>8</sup>

T. H. Morgan's mutant fly was a white-eyed male found in a population of normal red-eyed flies. Morgan had found a gene for eye color on what we now know as the X chromosome, a sex chromosome present in males in only a single copy, but in females in two copies. Using this mutation, he proved by various matings of mutant and normal flies that chromosomes determine sex, which had already been indicated by observing chromosomes through the microscope. This discovery marked the beginning of a demonstration of many of the

basic and universal facts of genetics. Morgan and his students introduced genetic mapping as a means to establish the order of genes on the chromosome; it is the basic technique used today to map the genes of human disease, such as Huntington's disease and cystic fibrosis.

Discoveries in genetics typically used inbred strains of animals, plants, and fungi with the particular species chosen for their tolerance to life in the laboratory. Morgan initially turned to inbred strains because animals from the wild, when mated, produced offspring with too much variation in their traits, such as wing size or eye color. But with this choice he turned from wild populations where the dynamics and variation of populations could be observed, to inbred laboratory strains where they could not. Variation, previously a source of fascination, was becoming an experimental nuisance. Selection was now performed in the laboratory by geneticists to identify traits that were easy to score, rather than traits that might be related to survival in the wild, or to embryonic development, or to evolution. The original impulse to understand how organisms evolved was lost.

Morgan and his group helped to initiate the modern field of experimental genetics. They found no evidence that genetic variation was directed; all their data were consistent with random genetic change. As a footnote, Morgan personally maintained his broad interest in developmental biology and evolution until his death in 1945. By 1928, when he moved from Columbia University to the California Institute of Technology, he gave up work on the fruit fly and turned again to issues of variation and individuality. None of his famous students followed this path.

### *The Last Hurrah for Facilitated Genetic Variation?*

By the dawn of molecular biology in the 1950s, there had been no credible evidence that an organism could specifically respond to an environmental stress by mutating a particular gene. But a well-designed molecular experiment disproving such a Lamarckian connection was lacking. To resolve this question once and for all, John Cairns, a well-known bacterial geneticist and biochemist, turned to the human gut

bacterium, *Escherichia coli*, which can be studied in large populations and over many generations.

Cairns asked if bacteria repaired a specific damaged gene at a higher rate when it was needed for growth than when it was not needed. Could the bacterium generate a heritable response to need, in the same way that giraffes extended their necks when they *needed* food that was out of reach? To the surprise of the scientific community, Cairns at first claimed evidence for directed genetic (Lamarckian) change. The bacterium repaired the gene by mutation (reversing or compensating for the initial DNA sequence change by further changes) at an accelerated rate if it needed the enzyme for growth, faced only with the alternative of starvation and eventual death.<sup>9</sup>

Though the gene was repaired, the critical question was whether it was modified more quickly than other genes that were not required for growth. With further analysis, it turned out that Cairns had badly misinterpreted his result: stressful starvation conditions increased the mutation rate for *all* genes, not just for the required gene. This increase of rate was an adaptation to the stress of starvation, which subsided when the bacterium grew again. Subtle technical reasons had completely fooled Cairns; once again, the search for Lamarckian inheritance had failed, here under conditions that many biologists considered the most favorable for finding it, if it existed.

After half a century of molecular biology, we still have found no mechanism that, as a physiological response of the mother or father to environmental stresses, modifies the genetic information of the egg or sperm. We know that various viruses can carry genetic information into cells, and this information can be incorporated into the cells' DNA, their permanent genetic dowry. The prevalence of viral sequences in the genome suggests that viruses at various times have entered the germ line from the outside. Again, there is no evidence that the genes carried by these viruses reflect any previous stress-related physiological response by the host.

Modern molecular and genetic analysis has revealed no hint of directed genetic change in response to physiological need or experience. No mechanism is known to direct a specific environmental stress

toward the alteration of a specific gene or set of genes, as a way to ameliorate that stress. Hence there is no evidence for “facilitated genotypic change.” Genetic variation and selection are completely uncoupled.

### The Modern Synthesis

By 1940 the liberation of genetic change from Lamarckian overtones (even without Cairns’s negative experiment) allowed leading evolutionary biologists to come together and proclaim a modern Darwinian theory, the Modern Synthesis. Close to Darwin in all important respects, it was now made consistent with contemporary science. Competing theories of evolution rapidly lost favor. The macromutations of de Vries had sunk to the status of a special case. Orthogenesis, a view that organisms evolve according to internally directed rather than externally selected paths, was simply a misinterpretation of the variation in existing populations. It was not so much false as it failed to offer any mechanism.

New traditions emerged with the study of wild populations, which drew on entirely Darwinian concepts. Population genetics resolved some problems that Mendelian genetics seemed to have created for traits that were continuous and quantitative rather than discrete, as well as explaining how a genetic change spreads in a population. Natural selection was given center place in sifting “profligate and chaotic” variation into the diversity of organismal forms we know.<sup>10</sup>

Stephen J. Gould argued that the Modern Synthesis had quickly hardened into a strictly adaptationist program, focusing on selective conditions and ignoring the role of the organism in generating phenotypic variation. By 1940 the fossil record had grown, and more and more gaps seemed to be filled. Although the record was known to be incomplete, it was surprisingly compatible with Darwin’s ideas. Several specimens of *Archaeopteryx* had been found (the first in 1861), and its partial reptile–partial bird traits seemed to imply a smooth progression toward birds as we know them, not a macromutational eruption of birds from reptiles.

Since 1940 at least 12 other relatives of intermediates of the reptile-bird lineage (feathered dinosaurs, miniraptors, and flying dinosaurs) have been unearthed—many in China in the 1990s, though none is quite like *Archaeopteryx*. A recently discovered example of a feathered dinosaur is shown in Figure 4. The assemblage of fossils suggests ordered changes in the feathers, reversal of the pubis bone in the pelvic region, reversal of the first toe, and reduction of vertebrae in the tail.

Yet in this worldview that saw all creativity in evolution as coming from selection, something was missing. It is as if a play had been written, the stage was set, but the cast had been forgotten. The organism and its role in creating variation were largely absent.<sup>11</sup>

The Modern Synthesis of 1940 was not so much wrong as it was incomplete. Biology itself had deeply split, perhaps making completion more difficult. The three great disciplines—genetics, developmental biology, and evolutionary biology—had gone separate ways. When new fields such as molecular biology and cell biology emerged, they had essentially no contact with evolutionary biology.<sup>12</sup>

The Mendelian understanding of heritable variation was the principal advance of the Modern Synthesis. Heritable variation was divided into two parts: variation in the genotype and variation in the phenotype. After making the important distinction that only the genotype is inherited but only the phenotype is selected, the Modern Synthesis reduced evolution to three basic steps. First, there was the occurrence of random genotypic variation—in modern parlance, a random modification of the sequence of DNA. Second, the change of genotype caused a change of phenotype within the individual organism (by means not specified). Third, the altered phenotype was selected (and with it the altered genotype required for it) on the basis of the individual's reproductive fitness, that is, its ability to contribute progeny to future generations.

On the question, of how the altered genotype caused an altered phenotype, the Modern Synthesis was silent. The old ideas of the environmental induction of variation had been purged. A key tenet of the synthesis was the independence of phenotypic variation from ambient selective conditions. Experience, learned behavior, or physiolog-



Figure 4 A feathered dinosaur: *Protarchaeopteryx* reconstructed from 125-million-year-old fossils from northeast China. Its length was 2 feet (70 cm). Having feather-like outgrowths from the integument, it is considered a member of a flightless dinosaur group sharing a common ancestor with birds. (Redrawn from Angela Milner, "Dino-Birds," Natural History Museum, London, 2002.)

ical adaptation to the environment could not be inherited. No explanation was offered to replace environmentally induced variation. The evolutionary biologists of the mid-twentieth century cannot be faulted for failing to explain variation, for only the first ingredients of an explanation were yet available. A molecular theory of genetics was 15 to 20 years away, and a molecular theory of comparative embryology would only come at the very end of the twentieth century. Instead, biologists might be faulted for their failure to recognize this large gap in their evolutionary theory. They mostly just ignored it.

Despite this omission, evolutionary biologists maintained strong views on the nature of phenotypic variation. Many thought that anything in the phenotype could change owing to random mutation. According to Gould, Darwin thought that variation must meet “three crucial requirements: copious in extent, small in range of departure from the mean, and isotropic” (or undirected toward adaptive needs of the organism). Gould called these three attributes of variation Darwin’s most brilliant insight, “because he realized that selection could not otherwise operate as the creative force in the evolution of novelties.” The alternative would have the organism generate a biased profusion of phenotypic variation for selection to act upon.<sup>13</sup>

The Modern Synthesis made the concept of adaptation paramount in evolutionary theory. The organism was like modeling clay, and remolding of the clay meant that each of the billions of little grains was free to move a little bit in any direction to generate a new form. This was close to saying that not only was the input of genotypic variation random but the output of phenotypic variation was random as well, or at least constrained very little. With this approach, the problem of how the processes of embryonic development and cellular function create the phenotype could be largely dismissed as interesting but not informative for evolutionary change, further segregating evolutionary biology from its peer disciplines. Selection alone might suffice to understand the succession of phenotypes that constitutes the history of evolutionary change. If an organism needed a wing, an opposable thumb, longer legs, webbed feet, or placental development, any of these would emerge under the proper selective conditions, with time.

The organism, it seemed, could be counted on to generate all of the variation needed for selection to act.

Some biologists later argued that the organism was constrained as to the kind of variation it could produce: rather than the full panoply of changes, some kinds would be missing. Perhaps some components of the organism were more difficult to change than others, and these would remain unchanged. Indeed, many conserved proteins and genes exist in the phenotype. In general, though, constraint was considered a minor effect, or trivial, for example, in explaining why mollusks and echinoderms were less able to evolve wings than vertebrates.

### Novelty, Time, and Random Mutation

What if evolutionary biologists were wrong to think of phenotypic variation as random and unconstrained, even though genetic variation was random and unconstrained? How much would it matter if we really understood how genetic variation leads to phenotypic variation, and in particular how facile or difficult is it to achieve a specific phenotype? Well, we could perhaps say we understand how evolutionary change occurs, based on the organism's capacity to generate novelty, without reference to particular selective conditions or catastrophic events. Also, we would be able to face the issue of the rate of evolution, which has always been imponderable. Skeptics of evolution, even in Darwin's time, said that the hypothesis of selection acting on variation certainly sounds reasonable, but there has not been enough time for suitable variants to arise. Organisms just could not generate bat wings and whale flippers by variation and selection in the twenty million years indicated by the fossil record. Shades of Paley's argument about the watch!

By comparison, if we question how long it would take a high-speed computer to write randomly a specific Shakespearean sonnet, we are asking that all the letters of the words of the sonnet will come up simultaneously in the correct order. It is an impossible task, even if all the computers in the world today had been working from the time of the big bang to the present. Even to compose the phrase, "To

be or not to be,” letter by letter, would take a typical computer millions of years.

Of course, the chance of coming up with a specific sentence or sonnet would improve vastly if selection or biased variation were introduced. On the selective side, we might accept provisionally a partial success such as “Tu is or no to iz” and then improve upon it—but that would already be lowering our selective requirements. Or we might keep individual correct letters as they arise, rather than waiting for all the correct ones to come up at once. Biasing variation can also improve the rate of outcome: if the computer generates only known words (using a dictionary) rather than random letter combinations, the process is accelerated. And if the computer generates only English words of three or fewer letters, the time to get the sentence is shortened to much less than a year. Thus, biasing variation should also have a huge effect on the speed of evolutionary change. Finally, if biased variation and piecemeal selection are combined, the required time can be very short.

Many evolutionary biologists dismiss the issue of rates of variation. They tell us that geological time is, in fact, very long when compared with the decades, centuries, or millennia that have sufficed for the divergence of domestic animals into grossly different breeds by artificial selection, or for the changed coloration of moths or beak size of finches via natural selection. Admitting all this, some skeptics are still not willing to grant that random variation can produce anything as complex as a flower or an eye, even over geological time, much less a human being from a bacterium-like organism.

Without some account of how complex novelty arises, mere refuge in the sufficiency of time is unconvincing. To comprehend fully how genotypic change generates phenotypic change, one needs an understanding of how the genotype generates the phenotype. A degree of understanding is coming where none was before, giving us a sense of the ultimate map between genotype and phenotype. That map should provide a way to estimate the feasibility of evolutionary change. The existing phenotype of the organism biases the realm of possible phenotypic variation: that much is self-evident. But how, how much, and

in what directions it biases novelty in evolution remain difficult and crucial questions.

### Toward a Theory of Facilitated *Phenotypic* Variation

As we have seen in this chapter, genetic variation is not channeled toward adaptation to selective conditions. Whatever bias there is to alter the amount and kind of phenotypic variation must arise out of the construction of the organism itself. Our theory about how organisms generate novelty in evolution starts with some assumptions which, though not in dispute, are not commonly appreciated.

First, genetic variation is required for evolutionary change. Genetic variation initially arises by mutation. Much of the genetic change that is important in evolution comes from the reassortment of mutations of previous generations by sexual reproduction.

Second, present-day organisms come from previous organisms, so they may retain remnants of the properties of their ancestors, including properties that allowed them to change in the past. A big surprise of modern biology has been conservation—that even distantly related organisms use similar processes for cellular function, development, and metabolism. Each process, comprised of many protein components working together, contributes to the phenotype. When a process is conserved, most of its protein components are conserved. Details of metabolism are the same in bacteria and humans; basic cell organization and function are similar between yeast and humans; and developmental strategies in fruit flies are strikingly similar to those in humans. The conservation of key processes in diverse organisms today implies, as we shall see, that we can deduce the basic physiological and developmental processes of organisms in the past. Even though these processes are not revealed by the fossil record, broad conservation among living organisms puts us in an unambiguous position to extrapolate back to our ancestors.

Third, all organisms are a mixture of conserved and nonconserved processes (said otherwise, of unchanging and changing processes), rather than a uniform collection of processes that change equally in

the course of evolution. Novelty in the organism's physiology, anatomy, or behavior arises mostly by the use of conserved processes in new combinations, at different times, and in different places and amounts, rather than by the invention of new processes.

We have not yet described the processes themselves, but we shall see that they can be used in many different contexts and to different degrees. This versatility, part of the remarkable adaptability of processes to conditions, is key to their special role in evolution. The surprisingly small number of genes for humans and other complex animal forms reflects the anatomical and physiological complexity that can be achieved by the reuse of gene products. The conserved processes are fundamentally cellular processes; they operate on many levels in the development and functioning of the organism. They are the *core processes* of the organism.

Central to our argument is that these processes, many of which have been conserved for hundreds of millions or even billions of years, have very special characteristics that facilitate evolutionary change. They have been conserved, we suggest, not merely because change in them would be lethal (although that might be a factor), but because they have repeatedly facilitated changes of certain kinds around them.

Many of the conserved core processes have the capacity to be easily linked together in new combinations. New linkages can occur with a minimum requirement for genetic change and hence can happen readily. A new combination of processes can arise with little or no change of the units themselves. We will talk later about the concept of weak regulatory linkage, which means essentially that links between processes can be forged without extensive retooling of each component. To maintain these links, processes are often reinforced with additional weak linkages—the suspender and belt approach to reliability.

Until we describe specific mechanisms, a metaphor may be useful. To double the size of Paley's brass pocket watch, virtually every component would have to be retooled, from the glass face to the brass gears. If growth of an animal involved such a process, it would be nearly impossible. The components of living things are more like Lego

blocks. Size and shape of the organism or an anatomical part of the organism can be varied by reusing common components in new combinations and amounts. The blocks do not change but their arrangement does. Linkages are readily made and broken.

In conjunction with the unchanging aspects of phenotype, we have also asked what really does change on a cellular and molecular level in evolution. It is not the conserved core processes. We argue that regulatory components are the main targets for heritable change—small features of the protein, RNA, or DNA that determine the time, circumstances, and degree of activity of the processes. These are often involved in controlling the linkage and activity of processes. Although the phenotype may play out at the gross anatomical and physiological level, the real locus of change is in the cellular processes that generate these anatomies and physiologies. Sewall Wright, the great population geneticist, said it most clearly: “The older writers on evolution were often staggered by the seeming necessity of accounting for the evolution of fine details . . . , for example, the fine structure of all the bones . . . Structure is never inherited as such, but merely types of adaptive cell behavior which lead to particular types of structure under particular conditions.”<sup>14</sup> It is remarkable that in 1931 Wright could foresee a time when it would be possible to explain anatomy and physiology in terms of the cell’s adaptive responses to differing conditions. We will show that such adaptability is built into most of the cell’s conserved core processes.

Why would organisms be constructed to facilitate evolutionary change? What is in it for them? There are several answers, but the most powerful is that organisms are always changing and responding to change. In the course of life, they alter their physiological state and behavior. They have mechanisms to resist extremes of temperature, to adapt to variations in the food and water supply, and to modify their response to predators. Some kinds of adaptability operate on a short time scale, such as the fight-or-flight response involving adrenalin secretion in threatening situations. Rapid changes occur in the heart rate, vascular system, and nervous system to mobilize reserves. The frightened organism is in a very different physiological state than the

secure one. Other kinds of adaptability operate over longer times, such as the acclimation of an animal to high altitude, and even longer-term adaptations of muscle and bone growth in response to repeated exercise or physical load. Physiological adaptability toward environmental change helps the organism survive.

Furthermore, adaptability of the organism is perhaps even more extensive toward the changing internal conditions wrought by embryonic development. Most of this developmental adaptability is invisible to us, because it is directed internally as one group of cells responds to signals from another. However, there are examples of developmental adaptability toward external conditions as well. Although physiological and developmental adaptations operate differently than evolutionary adaptations, they often entail the same cellular mechanisms. The road to evolutionary change is paved with physiological adaptability. Phenotypic variation, and along with it evolutionary change, is facilitated by simple regulatory tweaks to existing physiological and developmental processes that long ago were designed so that the organism could adapt to its environment.