The Plausibility *of* Life

Resolving Darwin's Dilemma

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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 processes. 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. Recognizing 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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INTRODUCTION

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.[1]

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.[2]

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.[3]

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).[4]

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.[5]

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 biologists 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.