

Molecular Machines: Experimental Support for the Design Inference

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Cosmic Pursuit

March 1, 1998

To Darwin, the cell-and every microbiological function-was an unknowable black box. Now that we can look into this box, can we apply Darwin's theory to it? Why is it that, of the thousands of papers published in science journals, none ever discuss detailed models for intermediates in the development of complex biomolecular structures? In drawing his ground-breaking conclusions, Behe is not inferring design from what we do not know, but from what we do know.

Darwinism's Prosperity

Within a short time after Charles Darwin published *The Origin of Species* the explanatory power of the theory of evolution was recognized by the great majority of biologists. The hypothesis readily resolved the problems of homologous resemblance, rudimentary organs, species abundance, extinction, and biogeography. The rival theory of the time, which posited creation of species by a supernatural being, appeared to most reasonable minds to be much less plausible, since it would have a putative Creator attending to details that seemed to be beneath His dignity.

As time went on the theory of evolution obliterated the rival theory of creation, and virtually all working scientists studied the biological world from a Darwinian perspective. Most educated people now lived in a world where the wonder and diversity of the biological kingdom were produced by the simple, elegant principle of natural selection.

However, in science a successful theory is not necessarily a correct theory. In the course of history there have also been other theories which achieved the triumph that Darwinism achieved, which brought many experimental and observational facts into a coherent framework, and which appealed to people's intuitions about how the world should work. Those theories also promised to explain much of the universe with a few simple principles. But,

by and large, those other theories are now dead.

A good example of this is the replacement of Newton's mechanical view of the universe by Einstein's relativistic universe. Although Newton's model accounted for the results of many experiments in his time, it failed to explain aspects of gravitation. Einstein solved that problem and others by completely rethinking the structure of the universe.

Similarly, Darwin's theory of evolution prospered by explaining much of the data of his time and the first half of the 20th century, but my article will show that Darwinism has been unable to account for phenomena uncovered by the efforts of modern biochemistry during the second half of this century. I will do this by emphasizing the fact that life at its most fundamental level is irreducibly complex and that such complexity is incompatible with undirected evolution.

A Series of Eyes

How do we see?

In the 19th century the anatomy of the eye was known in great detail and the sophisticated mechanisms it employs to deliver an accurate picture of the outside world astounded everyone who was familiar with them. Scientists of the 19th century correctly observed that if a person were so unfortunate as to be missing one of the eye's many integrated features, such as the lens, or iris, or ocular muscles, the inevitable result would be a severe loss of vision or outright blindness. Thus it was concluded that the eye could only function if it were nearly intact.

As Charles Darwin was considering possible objections to his theory of evolution by natural selection in *The Origin of Species* he discussed the problem of the eye in a section of the book appropriately entitled "Organs of extreme perfection and complication." He realized that if in one generation an organ of the complexity of the eye suddenly appeared, the event would be tantamount to a miracle. Somehow, for Darwinian evolution to be believable, the difficulty that the public had in envisioning the gradual formation of complex organs had to be removed.

Darwin succeeded brilliantly, not by actually describing a real pathway that evolution might have used in constructing the eye, but rather by pointing to a variety of animals that were known to have eyes of various constructions, ranging from a simple light sensitive spot to the complex vertebrate camera eye, and suggesting that the evolution of the human eye might have involved similar organs as intermediates.

But the question remains, how do we see? Although Darwin was able to persuade much of the world that a modern eye could be produced gradually from a much simpler structure, he did not even attempt to explain how the simple light sensitive spot that was his starting point actually worked. When discussing the eye Darwin dismissed the question of its ultimate mechanism by stating: "How a nerve comes to be sensitive to light hardly concerns us more than how life itself originated."

He had an excellent reason for declining to answer the question: 19th century science had not progressed to the point where the matter could

even be approached. The question of how the eye works—that is, what happens when a photon of light first impinges on the retina—simply could not be answered at that time. As a matter of fact, no question about the underlying mechanism of life could be answered at that time. How do animal muscles cause movement? How does photosynthesis work? How is energy extracted from food? How does the body fight infection? All such questions were unanswerable.

The Calvin and Hobbes Approach

Now, it appears to be a characteristic of the human mind that when it lacks understanding of a process, then it seems easy to imagine simple steps leading from nonfunction to function. A happy example of this is seen in the popular comic strip Calvin and Hobbes. Little boy Calvin is always having adventures in the company of his tiger Hobbes by jumping in a box and traveling back in time, or grabbing a toy ray gun and "transmogrifying" himself into various animal shapes, or again using a box as a duplicator and making copies of himself to deal with worldly powers such as his mom and his teachers. A small child such as Calvin finds it easy to imagine that a box just might be able to fly like an airplane (or something), because Calvin doesn't know how airplanes work.

A good example from the biological world of complex changes appearing to be simple is the belief in spontaneous generation. One of the chief proponents of the theory of spontaneous generation during the middle of the 19th century was Ernst Haeckel, a great admirer of Darwin and an eager popularizer of Darwin's theory. From the limited view of cells that 19th century microscopes provided, Haeckel believed that a cell was a "simple little lump of albuminous combination of carbon", not much different from a piece of microscopic Jell-O®. Thus it seemed to Haeckel that such simple life could easily be produced from inanimate material.

In 1859, the year of the publication of *The Origin of Species*, an exploratory vessel, the H.M.S. Cyclops, dredged up some curious-looking mud from the sea bottom. Eventually Haeckel came to observe the mud and thought that it closely resembled some cells he had seen under a microscope. Excitedly he brought this to the attention of no less a personage than Thomas Henry Huxley, Darwin's great friend and defender, who observed the mud for himself. Huxley, too, became convinced that it was *Urschleim* (that is, protoplasm), the progenitor of life itself, and Huxley named the mud *Bathybius haeckelii* after the eminent proponent of abiogenesis.

The mud failed to grow. In later years, with the development of new biochemical techniques and improved microscopes, the complexity of the cell was revealed. The "simple lumps" were shown to contain thousands of different types of organic molecules, proteins, and nucleic acids, many discrete subcellular structures, specialized compartments for specialized processes, and an extremely complicated architecture. Looking back from the perspective of our time, the episode of *Bathybius haeckelii* seems silly or downright embarrassing, but it shouldn't. Haeckel and Huxley were behaving naturally, like Calvin: since they were unaware of the complexity of cells, they found it easy to believe that cells could originate from simple mud.

Throughout history there have been many other examples, similar to that of

Haeckel, Huxley, and the cell, where a key piece of a particular scientific puzzle was beyond the understanding of the age. In science there is even a whimsical term for a machine or structure or process that does something, but the actual mechanism by which it accomplishes its task is unknown: it is called a "black box." In Darwin's time all of biology was a black box: not only the cell, or the eye, or digestion, or immunity, but every biological structure and function because, ultimately, no one could explain how biological processes occurred.

Biology has progressed tremendously due to the model that Darwin put forth. But the black boxes Darwin accepted are now being opened, and our view of the world is again being shaken.

Take our modern understanding of proteins, for example.

Proteins

In order to understand the molecular basis of life it is necessary to understand how things called "proteins" work. Proteins are the machinery of living tissue that builds the structures and carries out the chemical reactions necessary for life. For example, the first of many steps necessary for the conversion of sugar to biologically-usable forms of energy is carried out by a protein called hexokinase. Skin is made in large measure of a protein called collagen. When light impinges on your retina it interacts first with a protein called rhodopsin. A typical cell contains thousands and thousands of different types of proteins to perform the many tasks necessary for life, much like a carpenter's workshop might contain many different kinds of tools for various carpentry tasks.

What do these versatile tools look like? The basic structure of proteins is quite simple: they are formed by hooking together in a chain discrete subunits called amino acids. Although the protein chain can consist of anywhere from about 50 to about 1,000 amino acid links, each position can only contain one of 20 different amino acids. In this they are much like words: words can come in various lengths but they are made up from a discrete set of 26 letters.

Now, a protein in a cell does not float around like a floppy chain; rather, it folds up into a very precise structure which can be quite different for different types of proteins. Two different amino acid sequences-two different proteins-can be folded to structures as specific and different from each other as a three-eighths inch wrench and a jigsaw. And like the household tools, if the shape of the proteins is significantly warped then they fail to do their jobs.

The Eyesight of Man

In general, biological processes on the molecular level are performed by networks of proteins, each member of which carries out a particular task in a chain.

Let us return to the question, how do we see? Although to Darwin the primary event of vision was a black box, through the efforts of many biochemists an answer to the question of sight is at hand. The answer involves a long chain of steps that begin when light strikes the retina and a

photon is absorbed by an organic molecule called 11-cis-retinal, causing it to rearrange itself within picoseconds. This causes a corresponding change to the protein, rhodopsin, which is tightly bound to it, so that it can react with another protein called transducin, which in turn causes a molecule called GDP to be exchanged with a molecule called GTP.

To make a long story short, this exchange begins a long series of further bindings between still more specialized molecular machinery, and scientists now understand a great deal about the system of gateways, pumps, ion channels, critical concentrations, and attenuated signals that result in a current to finally be transmitted down the optic nerve to the brain, interpreted as vision. Biochemists also understand the many chemical reactions involved in restoring all these changed or depleted parts to make a new cycle possible.

To Explain Life

Although space doesn't permit me to give the details of the biochemistry of vision here, I have given the steps in my talks. Biochemists know what it means to "explain" vision. They know the level of explanation that biological science eventually must aim for. In order to say that some function is understood, every relevant step in the process must be elucidated. The relevant steps in biological processes occur ultimately at the molecular level, so a satisfactory explanation of a biological phenomenon such as sight, or digestion, or immunity, must include a molecular explanation.

It is no longer sufficient, now that the black box of vision has been opened, for an "evolutionary explanation" of that power to invoke only the anatomical structures of whole eyes, as Darwin did in the 19th century and as most popularizers of evolution continue to do today. Anatomy is, quite simply, irrelevant. So is the fossil record. It does not matter whether or not the fossil record is consistent with evolutionary theory, any more than it mattered in physics that Newton's theory was consistent with everyday experience. The fossil record has nothing to tell us about, say, whether or how the interactions of 11-cis-retinal with rhodopsin, transducin, and phosphodiesterase could have developed, step by step.

"How a nerve comes to be sensitive to light hardly concerns us more than how life itself originated", said Darwin in the 19th century. But both phenomena have attracted the interest of modern biochemistry in the past few decades. The story of the slow paralysis of research on life's origin is quite interesting, but space precludes its retelling here. Suffice it to say that at present the field of origin-of-life studies has dissolved into a cacophony of conflicting models, each unconvincing, seriously incomplete, and incompatible with competing models. In private even most evolutionary biologists will admit that science has no explanation for the beginning of life.

The same problems which beset origin-of-life research also bedevil efforts to show how virtually any complex biochemical system came about. Biochemistry has revealed a molecular world which stoutly resists explanation by the same theory that has long been applied at the level of the whole organism. Neither of Darwin's black boxes-the origin of life or the origin of vision (or other complex biochemical systems)-has been accounted for by his theory.

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Irreducible Complexity

In *The Origin of Species* Darwin stated:

If it could be demonstrated that any complex organ existed which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down.

A system which meets Darwin's criterion is one which exhibits irreducible complexity. By irreducible complexity I mean a single system which is composed of several interacting parts that contribute to the basic function, and where the removal of any one of the parts causes the system to effectively cease functioning. An irreducibly complex system cannot be produced directly by slight, successive modifications of a precursor system, since any precursor to an irreducibly complex system is by definition nonfunctional.

Since natural selection requires a function to select, an irreducibly complex biological system, if there is such a thing, would have to arise as an integrated unit for natural selection to have anything to act on. It is almost universally conceded that such a sudden event would be irreconcilable with the gradualism Darwin envisioned. At this point, however, "irreducibly complex" is just a term, whose power resides mostly in its definition. We must now ask if any real thing is in fact irreducibly complex, and, if so, then are any irreducibly complex things also biological systems?

Consider the humble mousetrap (Figure 1). The mousetraps that my family uses in our home to deal with unwelcome rodents consist of a number of parts. There are: 1) a flat wooden platform to act as a base; 2) a metal hammer, which does the actual job of crushing the little mouse; 3) a wire spring with extended ends to press against the platform and the hammer when the trap is charged; 4) a sensitive catch which releases when slight pressure is applied, and 5) a metal bar which holds the hammer back when the trap is charged and connects to the catch. There are also assorted staples and screws to hold the system together.

If any one of the components of the mousetrap (the base, hammer, spring, catch, or holding bar) is removed, then the trap does not function. In other words, the simple little mousetrap has no ability to trap a mouse until several separate parts are all assembled.

Because the mousetrap is necessarily composed of several parts, it is irreducibly complex. Thus, irreducibly complex systems exist.

Molecular Machines

Now, are any biochemical systems irreducibly complex? Yes, it turns out that many are.

Earlier we discussed proteins. In many biological structures proteins are simply components of larger molecular machines. Like the picture tube, wires, metal bolts and screws that comprise a television set, many proteins are part of structures that only function when virtually all of the components have been assembled.

A good example of this is a cilium. Cilia are hairlike organelles on the surfaces of many animal and lower plant cells that serve to move fluid over the cell's surface or to "row" single cells through a fluid. In humans, for example, epithelial cells lining the respiratory tract each have about 200 cilia that beat in synchrony to sweep mucus towards the throat for elimination.

A cilium consists of a membrane-coated bundle of fibers called an axoneme. An axoneme contains a ring of 9 double microtubules surrounding two central single microtubules. Each outer doublet consists of a ring of 13 filaments (subfiber A) fused to an assembly of 10 filaments (subfiber B). The filaments of the microtubules are composed of two proteins called alpha and beta tubulin. The 11 microtubules forming an axoneme are held together by three types of connectors: subfibers A are joined to the central microtubules by radial spokes; adjacent outer doublets are joined by linkers that consist of a highly elastic protein called nexin; and the central microtubules are joined by a connecting bridge. Finally, every subfiber A bears two arms, an inner arm and an outer arm, both containing the protein dynein.

But how does a cilium work? Experiments have indicated that ciliary motion results from the chemically-powered "walking" of the dynein arms on one microtubule up the neighboring subfiber B of a second microtubule so that the two microtubules slide past each other (Figure 2). However, the protein cross-links between microtubules in an intact cilium prevent neighboring microtubules from sliding past each other by more than a short distance. These cross-links, therefore, convert the dynein-induced sliding motion to a bending motion of the entire axoneme.

Now, let us sit back, review the workings of the cilium, and consider what it implies. Cilia are composed of at least a half dozen proteins: alpha-tubulin, beta-tubulin, dynein, nexin, spoke protein, and a central bridge protein. These combine to perform one task, ciliary motion, and all of these proteins must be present for the cilium to function. If the tubulins are absent, then there are no filaments to slide; if the dynein is missing, then the cilium remains rigid and motionless; if nexin or the other connecting proteins are missing, then the axoneme falls apart when the filaments slide.

What we see in the cilium, then, is not just profound complexity, but it is also irreducible complexity on the molecular scale. Recall that by "irreducible complexity" we mean an apparatus that requires several distinct components for the whole to work. My mousetrap must have a base, hammer, spring, catch, and holding bar, all working together, in order to function. Similarly, the cilium, as it is constituted, must have the sliding filaments, connecting proteins, and motor proteins for function to occur. In the absence of any one of those components, the apparatus is useless.

The components of cilia are single molecules. This means that there are no more black boxes to invoke; the complexity of the cilium is final, fundamental. And just as scientists, when they began to learn the complexities of the cell, realized how silly it was to think that life arose spontaneously in a single step or a few steps from ocean mud, so too we now realize that the complex cilium can not be reached in a single step or a few steps.

But since the complexity of the cilium is irreducible, then it can not have functional precursors. Since the irreducibly complex cilium can not have functional precursors it can not be produced by natural selection, which requires a continuum of function to work. Natural selection is powerless when there is no function to select. We can go further and say that, if the cilium can not be produced by natural selection, then the cilium was designed.

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A Non-Mechanical Example

A non-mechanical example of irreducible complexity can be seen in the system that targets proteins for delivery to subcellular compartments. In order to find their way to the compartments where they are needed to perform specialized tasks, certain proteins contain a special amino acid sequence near the beginning called a "signal sequence."

As the proteins are being synthesized by ribosomes, a complex molecular assemblage called the signal recognition particle or SRP, binds to the signal sequence. This causes synthesis of the protein to halt temporarily. During the pause in protein synthesis the SRP is bound by the trans-membrane SRP receptor, which causes protein synthesis to resume and which allows passage of the protein into the interior of the endoplasmic reticulum (ER). As the protein passes into the ER the signal sequence is cut off.

For many proteins the ER is just a way station on their travels to their final destinations. Proteins which will end up in a lysosome are enzymatically "tagged" with a carbohydrate residue called mannose-6-phosphate while still in the ER. An area of the ER membrane then begins to concentrate several proteins; one protein, clathrin, forms a sort of geodesic dome called a coated vesicle which buds off from the ER. In the dome there is also a receptor protein which binds to both the clathrin and to the mannose-6-phosphate group of the protein which is being transported. The coated vesicle then leaves the ER, travels through the cytoplasm, and binds to the lysosome through another specific receptor protein. Finally, in a maneuver involving several more proteins, the vesicle fuses with the lysosome and the protein arrives at its destination.

During its travels our protein interacted with dozens of macromolecules to achieve one purpose: its arrival in the lysosome. Virtually all components of the transport system are necessary for the system to operate, and therefore the system is irreducible. And since all of the components of the system are comprised of single or several molecules, there are no black boxes to invoke. The consequences of even a single gap in the transport chain can be seen in the hereditary defect known as I-cell disease. It results from a deficiency of the enzyme that places the mannose-6-phosphate on proteins to be targeted to the lysosomes. I-cell disease is characterized by progressive retardation, skeletal deformities, and early death.

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The Study of "Molecular Evolution"

Other examples of irreducible complexity abound, including aspects of protein transport, blood clotting, closed circular DNA, electron transport, the bacterial flagellum, telomeres, photosynthesis, transcription regulation, and much more. Examples of irreducible complexity can be found on virtually every page of a biochemistry textbook. But if these things cannot be explained by Darwinian evolution, how has the scientific community regarded these phenomena of the past forty years?

A good place to look for an answer to that question is in the *Journal of Molecular Evolution*. JME is a journal that was begun specifically to deal with the topic of how evolution occurs on the molecular level. It has high scientific standards, and is edited by prominent figures in the field. In a recent issue of JME there were published eleven articles; of these, all eleven were concerned simply with the analysis of protein or DNA sequences. None of the papers discussed detailed models for intermediates in the development of complex biomolecular structures.

In the past ten years JME has published 886 papers. Of these, 95 discussed the chemical synthesis of molecules thought to be necessary for the origin of life, 44 proposed mathematical models to improve sequence analysis, 20 concerned the evolutionary implications of current structures, and 719 were analyses of protein or polynucleotide sequences. However, there weren't any papers discussing detailed models for intermediates in the development of complex biomolecular structures. This is not a peculiarity of JME. No papers are to be found that discuss detailed models for intermediates in the development of complex biomolecular structures in the *Proceedings of the National Academy of Science*, *Nature*, *Science*, the *Journal of Molecular Biology* or, to my knowledge, any journal whatsoever.

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Sequence comparisons overwhelmingly dominate the literature of molecular evolution. But sequence comparisons simply can't account for the development of complex biochemical systems any more than Darwin's comparison of simple and complex eyes told him how vision worked. Thus in this area science is mute.

Detection of Design

What's going on? Imagine a room in which a body lies crushed, flat as a pancake. A dozen detectives crawl around, examining the floor with magnifying glasses for any clue to the identity of the perpetrator. In the middle of the room next to the body stands a large, gray elephant. The detectives carefully avoid bumping into the pachyderm's legs as they crawl, and never even glance at it. Over time the detectives get frustrated with their lack of progress but resolutely press on, looking even more closely at the floor. You see, textbooks say detectives must "get their man," so they never consider elephants.

There is an elephant in the roomful of scientists who are trying to explain the development of life. The elephant is labeled "intelligent design." To a person who does not feel obliged to restrict his search to unintelligent causes, the straightforward conclusion is that many biochemical systems were designed. They were designed not by the laws of nature, not by chance and necessity. Rather, they were planned. The designer knew what the systems would look like when they were completed; the designer took steps to bring the systems about. Life on earth at its most fundamental level, in its most critical components, is the product of intelligent activity.

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The conclusion of intelligent design flows naturally from the data itself-not from sacred books or sectarian beliefs. Inferring that biochemical systems were designed by an intelligent agent is a humdrum process that requires no new principles of logic or science. It comes simply from the hard work that biochemistry has done over the past forty years, combined with consideration of the way in which we reach conclusions of design every day.

What is "design"? Design is simply the purposeful arrangement of parts. The scientific question is how we detect design. This can be done in various ways, but design can most easily be inferred for mechanical objects.

Systems made entirely from natural components can also evince design. For example, suppose you are walking with a friend in the woods. All of a sudden your friend is pulled high in the air and left dangling by his foot from a vine attached to a tree branch.

After cutting him down you reconstruct the trap. You see that the vine was wrapped around the tree branch, and the end pulled tightly down to the ground. It was securely anchored to the ground by a forked branch. The branch was attached to another vine-hidden by leaves-so that, when the trigger-vine was disturbed, it would pull down the forked stick, releasing the spring-vine. The end of the vine formed a loop with a slipknot to grab an appendage and snap it up into the air. Even though the trap was made completely of natural materials you would quickly conclude that it was the product of intelligent design.

Intelligent design is a good explanation for a number of biochemical systems, but I should insert a word of caution. Intelligent design theory has to be seen in context: it does not try to explain everything. We live in a complex world where lots of different things can happen. When deciding how various rocks came to be shaped the way they are a geologist might consider a whole range of factors: rain, wind, the movement of glaciers, the activity of moss and lichens, volcanic action, nuclear explosions, asteroid impact, or the hand of a sculptor. The shape of one rock might have been determined primarily by one mechanism, the shape of another rock by another mechanism.

Similarly, evolutionary biologists have recognized that a number of factors might have affected the development of life: common descent, natural selection, migration, population size, founder effects (effects that may be due to the limited number of organisms that begin a new species), genetic drift (spread of "neutral," nonselective mutations), gene flow (the incorporation of genes into a population from a separate population), linkage (occurrence of two genes on the same chromosome), and much more. The fact that some biochemical systems were designed by an intelligent agent does not mean that any of the other factors are not operative, common, or important.

Conclusion

It is often said that science must avoid any conclusions which smack of the supernatural. But this seems to me to be both bad logic and bad science. Science is not a game in which arbitrary rules are used to decide what explanations are to be permitted. Rather, it is an effort to make true statements about physical reality. It was only about sixty years ago that the expansion of the universe was first observed. This fact immediately suggested a singular event-that at some time in the distant past the universe began expanding from an extremely small size.

To many people this inference was loaded with overtones of a supernatural event-the creation, the beginning of the universe. The prominent physicist A.S. Eddington probably spoke for many physicists in voicing his disgust with such a notion:

Philosophically, the notion of an abrupt beginning to the present order of Nature is repugnant to me, as I think it must be to most; and even those

who would welcome a proof of the intervention of a Creator will probably consider that a single winding-up at some remote epoch is not really the kind of relation between God and his world that brings satisfaction to the mind.

Nonetheless, the big bang hypothesis was embraced by physics and over the years has proven to be a very fruitful paradigm. The point here is that physics followed the data where it seemed to lead, even though some thought the model gave aid and comfort to religion. In the present day, as biochemistry multiplies examples of fantastically complex molecular systems, systems which discourage even an attempt to explain how they may have arisen, we should take a lesson from physics. The conclusion of design flows naturally from the data; we should not shrink from it; we should embrace it and build on it.

We are not inferring design from what we do not know, but from what we do know. We are not inferring design to account for a black box, but to account for an open box.

In concluding, it is important to realize that we are not inferring design from what we do not know, but from what we do know. We are not inferring design to account for a black box, but to account for an open box. A man from a primitive culture who sees an automobile might guess that it was powered by the wind or by an antelope hidden under the car, but when he opens up the hood and sees the engine he immediately realizes that it was designed. In the same way biochemistry has opened up the cell to examine what makes it run and we see that it, too, was designed.

It was a shock to the people of the 19th century when they discovered, from observations science had made, that many features of the biological world could be ascribed to the elegant principle of natural selection. It is a shock to us in the twentieth century to discover, from observations science has made, that the fundamental mechanisms of life cannot be ascribed to natural selection, and therefore were designed. But we must deal with our shock as best we can and go on. The theory of undirected evolution is already dead, but the work of science continues.

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