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Evolution and the Illusion of Randomness

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***Editor's Note**: This is the fourth in a set of essays by Mr. Talbott dealing with the new understanding of living organisms being urged upon us by the intense ongoing work in molecular biology. The previous installments were "Getting Over the Code Delusion" (Summer 2010), "The Unbearable Wholeness of Beings" (Fall 2010), and "What Do Organisms Mean?" (Winter 2011).*

Most biologists, I suspect, will happily own up to the fact that they think of the organism as engaged in strikingly directed and meaningful activity. The lion stalking the gazelle, the bird building a nest, the larva spinning a cocoon, the rose flowering, the cell dividing and differentiating, the organism maintaining its own way of being amid the perturbations of its environment—they all reflect a kind of intentional pursuit we would never attribute to dust, rocks, ocean waves, or clouds.

Biologists, that is, will acknowledge that, at molecular and higher levels, they see almost nothing but an effective employment of a thousand interwoven means to achieve a thousand interwoven ends—all in an almost incomprehensibly organized, coordinated, and integrated fashion expressing the striving of the organism as a whole. The organism, they will say, as it develops from embryo to adult—as it socializes, eats, plays, fights, heals its wounds, communicates, and reproduces—is the most concertedly purposeful entity we could possibly imagine. It does not merely exist in accord with the laws of physics and chemistry; rather, it is telling the meaningful story of its own life.

And then they will take it all back.

In other words, the routine language of biological description, highlighted in the earlier parts of this series, is fully accepted, only to be effectively disowned. The explanation for this remarkable intellectual flexibility lies in a widespread view that runs as follows. Evolution produces organisms that we cannot help describing as purposeful and meaningful agents. That is because natural selection tends to select organisms that are *fit*—well-adapted

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to their environments and "designed" for surviving and reproducing. When organisms have features that are adapted *for* something, we naturally see these features as meaningful and purposeful. And an organism compounded of such features seems to be an agent with a goal of some sort; if nothing else, it seems to act intentionally in order to survive and reproduce.

This agency, however, is said to be more a matter of *appearance* than of fundamental reality. While meaning and purpose may (somehow) "emerge" during the course of evolution, they emerge from processes that, at the most basic level of explanation and understanding, know nothing of them. Certainly—as the rather strange conviction runs—meaning and purpose play no role in the evolutionary "mechanisms" that have so expertly given rise to them.

Perhaps the brashest and most publicly effective advertisements for this entrenched view have arisen from Richard Dawkins and Daniel Dennett. Dawkins is a biologist and award-winning popularizer of conventional evolutionary thought, having produced such bestsellers as *The Selfish Gene* (1976) and *The Blind Watchmaker* (1986). Dennett, philosopher and deconstructor of consciousness, wrote about evolution in his widely influential book, *Darwin's Dangerous Idea: Evolution and the Meanings of Life* (1995). The two authors immensely admire each other's work.

Dennett, in one of his characteristic remarks, assures us that "through the microscope of molecular biology, we get to witness the birth of *agency*, in the first macromolecules that have enough complexity to 'do things.' … There is something alien and vaguely repellent about the quasi-agency we discover at this level—all that purposive hustle and bustle, and yet *there's nobody home.*" Then, after describing a marvelous bit of highly organized and seemingly meaningful biological activity, he concludes:

> Love it or hate it, phenomena like this exhibit the heart of the power of the Darwinian idea. An impersonal, unreflective, robotic, mindless little scrap of molecular machinery is the ultimate basis of all the agency, and hence meaning, and hence consciousness, in the universe.[1]

Or, we can listen to Dawkins: "Wherever in nature there is a sufficiently powerful illusion of good design for some purpose, natural selection is the only known mechanism that can account for it."[2] And: "Natural selection, the blind, unconscious, automatic process which Darwin discovered, and which we now know is the explanation for the existence and apparently purposeful form of all life, has no purpose in mind. It has no mind and no mind's eye. It does not plan for the future. It has no vision, no foresight, no sight at all."[3]

The general idea, then, looks something like this:

- The true nature of things is evident only at the bottom, and so we must understand life from the bottom up.

- What we find at the bottom are scraps of molecular machinery.

- Through the power of natural selection—which operates like a mindlessly mechanistic algorithm (Dennett) or a blind, unconscious automatism (Dawkins)—these low-level molecular machines slowly evolve into the kind of *apparently* purposeful, complex entities we recognize as organisms, including ourselves.

- Whatever we are to make of this appearance of meaning and purpose—including my own intentions as I write this and yours as you read it—we are both urged to shed our prejudices and acknowledge that we with our intentions somehow arise from more basic, underlying processes that are essentially dumb, meaningless, and mindless.

Of course, questions come to mind. Is the universe so schizoid or compartmentalized that any truth we observe at the "bottom" (whatever that means) must be proclaimed real, while the truth at other levels is unreal and illusory? This would be a particularly odd position to take in biology, where characteristic explanation runs from higher-level context to lower-level part (as we saw in the previous installments "The Unbearable Wholeness of Beings" [Fall 2010] and "What Do Organisms Mean?" [Winter 2011]). And if we really did find the root essence of things only at the bottom, then where would we locate Dennett's presumed scraps of mindless machinery amid the extraordinarily non-machine-like (and indeed scarcely material) quantum weirdness that has so preoccupied physicists for the past century? Physicists are the last people in the world with reason to claim mechanistic behavior at the bottom—and, in fact, some among them have long been driven by their own subject matter to reflect upon the *mindful* universe.[4]

As for the organism: are its apparently meaningful strivings meaningful or not? If they are not—if, for example, the appearance of purpose is an "illusion," as Dawkins puts it—then what is the difference between merely illusory purpose and the real thing? Perhaps he will say that there is *only* illusion. But then, if there is nothing for the illusion to be a convincing illusion *of,* it hardly makes sense to say it is an illusion at all, as opposed to being

just what it seems to be. On the other hand, if Dawkins admits that meaning and purpose actually exist as realities and are therefore available to be mimicked in an illusory way, what grounds does he have for claiming meaninglessness and purposelessness as fundamental to the world's character?

Letting the Reality of the Organism Speak

But while questions such as these do point to an extraordinary slipperiness in the remarks of Dawkins and Dennett, I do not intend to pursue the endless argument to which they would doubtless lead. There is a more fruitful way to assess the claims of mindless mechanism and illusion, and that is simply by comparing them to living creatures, especially at the molecular level that so impresses these writers as being both fundamental and rooted in meaninglessness.

Dennett's contention that through the microscope we "witness the birth of *agency*, in the first macromolecules that have enough complexity to 'do things'" is itself an illusion. Neither he nor anyone else has ever witnessed the birth of such agency through a microscope or any other instrument—a fact that many decades of unrestrained speculation about the creation of life some billions of years ago does nothing to change. What we see through the microscope is what we see with our unaided eyes: life comes from life. Living cells, with all their displays of agency, come from other living cells. Open any journal of any sub-sub-subdiscipline of biology, and you will immediately be overwhelmed by suggestions of *agency* even at the lowest levels. Molecules, we are told to a fault, are bent on regulating, signaling, stimulating, responding, controlling, assisting, suppressing, healing, repairing, sensing, coordinating—and all in a way that can be understood only contextually. There is nothing at *any* level of observation, whether above or below macromolecules, that is not caught up in the meaningful life of the organism as a whole.

Living agency is, if anything, even more vivid when we shift our attention to evolution and consider what passes from one generation to the next—for example, through "simple" cell division and mitosis (processes of almost unfathomable complexity) or through the even more elaborately orchestrated fugue we know as meiosis in sexual reproduction. In the latter case, everything comes to an intense focus in the sublime performance that one pair of authors describes as "Chromosome Choreography: The Meiotic Ballet."[5] Nowhere does the cell seem more intent on moving toward a definite end than in the intricately coordinated steps of this ballet. And so a path is prepared from one generation to the next. Life engenders life.

This unbroken thread of life explains why we encounter the language of meaning and purpose that the biologist breathes into every description of every organism. Everything characteristic of the organism, from its behavior as a whole down through the performance of its various organs all the way to the micro-world of interwoven molecular processes in the cell—that is, everything distinctively *biological* as opposed to merely physical and chemical—can only be described, and always is described, in a language of coordinated processes, governing norms, and means brought into the service of ends. We are never talking merely about physical and chemical interactions, but rather about processes continually shifting, transforming, and adjusting themselves in relation to their context in order to *go somewhere*, if only to hold themselves within reasonable distance of some particular state (as when warm-blooded creatures maintain their internal temperature within a certain range). And this kind of *going* or *maintaining* ceases upon death, when everything takes on an entirely different, non-living character.

Such, then, is the living reality that Dawkins refers to as the "appearance of design" or the "illusion of design and planning."[6] It is also what Dennett has in mind when he writes, "All the Design in the universe can be explained as the product of a process that is ultimately bereft of intelligence, in other words an algorithmic process that weds randomness and selection to produce…all the intelligence that exists."[7] (Dawkins and Dennett sometimes seem fixated upon design, presumably as a result of their severely constraining preoccupation with religion and with the "creationism" or "intelligent design" promulgated by some religious folks. Although the word has its legitimate uses, you will not find me speaking of design, simply because—as I've made abundantly clear in previous articles—organisms cannot be understood as having been designed, machine-like, whether by an engineer-God or a Blind Watchmaker elevated to god-like status. If organisms participate in a higher life, it is a participation that works from within—at a deep level the ancients recognized as that of the *logos* informing all things. It is a sharing of the springs of life and being, not a mere receptivity to some sort of external mechanical tinkering modeled anthropocentrically on human engineering.)

Dawkins and Dennett's stance is bizarre—above all, because *everything* in the drama of evolution presupposes the meaning-soaked activity of the organisms whose meaning is said to be explained away. The organism reproduces itself by bringing all its choreographic powers of organization, coordination, and integration to bear upon the reproductive process; only so do we have a passage from one generation to another. And only so

does natural selection (which itself involves nothing other than a living, intensely directed engagement of organisms with each other in an environment partly of their own making) gain material to work on.

Where, then, do we find dumb, lifeless mechanisms blindly engendering new life forms? Where do we see anything other than the elaborate, interwoven, overwhelmingly meaningful activity of living beings, playing out at every level, from the molecular to the ecological?

Chance to the Rescue?

One answer will occur immediately to anyone properly educated in conventional evolutionary theory: random mutation—the arbitrary change of an organism's genomic sequence—is what most obviously happens blindly. This is the sort of change that used to be routinely evoked by mentioning the mutagenic effects of cosmic rays—the impacts of "blind chance" that are supposed to provide the raw material for natural selection to act upon. (In addition to natural selection, I could speak of other processes often considered to be "forces" of evolution—migration, physical constraints upon development, genetic drift, assortative mating, and so on—but none of this would alter the course of my argument. As for "mutation," it will become evident that I use the term broadly to include recombination and other sorts of genetic change. I should also mention that this essay focuses upon more complex organisms, often citing work on mammals and humans. There are other stories, equally dramatic, to be told at the lower end of the scale of complexity.)

Of course, every creature spends a lifetime encountering unpredictable impacts from its environment. No one would say in general that such encounters, even if they were truly "random" in some sense, overcome the coherent, insistent, and distinctive life of the organism; rather, they are occasions for expressing that life. Engagement with the never fully predictable larger environment is what life is about, and it always happens in a way that is influenced, not only by the environment, but also by the preferred way of being of the organism. A great deal hinges upon how the organism takes up the things it encounters. Randomness in environmental encounters (if the idea makes any sense at all) does not imply randomness in the organism. This applies as much to cosmic-ray encounters as to buffetings by the wind or attacks by predators.

All we can possibly mean by "random occurrences" relative to an organism is "occurrences that have not yet been woven into the meaningful life story of the organism." And even before any such weaving takes

place, the idea that an event is "random" only perplexes our understanding. We are immersed in—we participate moment by moment in—a world that is ordered and full of meaning, and it is hard to see how we can detach ourselves so fully from our context as to encounter something wholly "out of context."

As for genetic mutations specifically, the crucial point was already made by Oxford University biophysicist Norman D. Cook in 1977: "Biological intervention through enzymes and enzyme systems is the principal mechanism of *in vivo* mutation." Biologists commonly interpret such mutations as random errors in vital processes such as DNA replication, but "if…changes in the genetic material are indeed mediated by other cellular molecules, then the idea of 'randomness' lacks all but the most trivial descriptive meaning, referring only to *our knowledge* of the mutation event."[8] Furthermore, as British radiologist B. A. Bridges pointed out: even studies of radiation-induced mutation in bacteria have shown that cellular repair systems are "necessary for nearly all of the mutagenic effect of ultraviolet and around 90 percent of that of ionizing radiation."[9]

That is, outcomes depend at least in part on what the organism *does* with the influences impinging upon it. You might think that radiation mostly causes very local alterations in DNA, corresponding to the immediate location of damage. Yet the great majority of radiation-induced mutations involve large regions of DNA, often encompassing more than an entire gene spanning thousands of nucleotide base pairs, or letters, of the genetic sequence.[10] The organism making such changes is apparently prepared to respond as best it can and in its own way when it engages these potentially harmful elements of its environment.

Despite the fact that early work on ionizing radiation "provided the genetic basis for" modern evolutionary theory and quickly became "a theoretical cure-all for the difficult problem of genetic diversity" (Cook's phrases), this particular cause of mutation hardly figures centrally in the broad literature on genetic change today. There are simply too many other relevant processes going on—and none of them looks like the cosmic-ray activity whose misconstrual as a kind of archetype of randomness was so vital to the formulation of evolutionary theory.

In fact, we are no longer free to imagine that evolution waits around for "accidents" to knock genes askew so as to provide new material for natural selection to work on. The genome of every organism is actively and insistently remodeled as an expression of its context. Genetic sequences get rewritten, reshuffled, duplicated, turned backward, "invented" from scratch, and otherwise revised in a way that prominently advertises the

organism's accomplished skill in matters of genomic change. The illustrations of this skill are so extensive in the contemporary literature that there is no way to review it adequately here. (For some examples, see the supplement "Natural Genome Engineering" [page 53], which contains the bulk of the evidence for my contentions here.)

And regardless of the source of mutation, or genetic change, one cannot ignore the explosively growing literature on how genes actually function within gene regulation networks. A mutation is subject not only to elaborate processes that repair, modify, or ignore the mutation, but also to regulatory networks that respond to the mutated gene according to the logic of the larger need. You will recall from a previous article how an organic context can retain a certain stable character in the face of relatively wide-ranging variations or disturbances in its lower-level constituent processes. Molecular biologists have discovered in studies with a number of organisms, including mice, that "knocking out" (disabling or mutating) both copies of a gene with important functions can in many circumstances leave the organism seemingly unimpaired and functioning normally.[11]

But even leaving aside all the contextually coherent revision and all the *meaning-making* that bends the apparently random to the organism's own purposes, we find that strictly low-level analyses show mutations to be nonrandom. The point isn't disputed by anyone, and current research aimed at elucidating all the factors conducive to genomic change is steadily expanding our field of view, with huge implications for evolutionary theory. This leaves but one last refuge for those who would persuade us that the mutational element of evolutionary change is blind, lifeless, and meaningless. Their argument runs this way:

> Mutations are commonly said to occur "randomly." However…mutations do not occur at random with respect to genomic location and gender, nor do all types of mutations occur with equal frequency. So, what aspect of mutation is random? Mutations are claimed to be random in respect to their effect on the fitness of the organism carrying them. That is, any given mutation is expected to occur with the same frequency under conditions in which this mutation confers an advantage on the organism carrying it, as under conditions in which this mutation confers no advantage or is deleterious.[12]

Or as Douglas Futuyma, distinguished professor of ecology and evolution at the State University of New York at Stony Brook, once put it: "Mutation is random in [the sense] that the chance that a specific mutation will occur is not affected by how useful that mutation would be."[13]

So not even mutations, it turns out, are really random. There is only one crucial respect in which we need to declare them random if we would reduce to an illusion the meaningful coherence of all the rest of life: they are (in the special sense just given) random with respect to their effects upon fitness, and therefore in their evolutionary role. So runs the prevailing belief.

Is there any excuse for the huge burden of meaninglessness attached to the slender thread of presumed chance epitomized in cosmic rays—or is this sense of meaninglessness merely an illusory spell woven by evolutionary biologists? More particularly, does the concept of randomness gain clarity when we set it, as we are advised to do, beside that of fitness? We will see.

Can We Track Fitness?

Fitness is usually taken to comprise all those traits affecting the organism's ability to survive and produce viable offspring in its particular environment. But immediately we run into difficulties. In the 1970s, journalist Tom Bethell illustrated a small part of the problem this way:

> A mutation that enables a wolf to run faster than the pack only enables the wolf to survive better if it does, in fact, survive better. But such a mutation could also result in the wolf outrunning the pack a couple of times and getting first crack at the food, then abruptly dropping dead of a heart attack, because the extra power in its legs placed an extra strain on its heart.[14]

Or perhaps, by outrunning its pack, the wolf would be more subject to the dangers of hoof or horn from a threatened animal—an animal that for a moment need not worry about more than one wolf. But this is hardly to begin a recital of the difficulties in assessing the fitness of any particular change. In a now-classic article, Harvard geneticist and evolutionary theorist Richard Lewontin once illustrated the near-impossibility of making judgments about fitness:

> A zebra having longer leg bones that enable it to run faster than other zebras will leave more offspring only if escape from predators is really the problem to be solved, if a slightly greater speed will really decrease the chance of being taken and if longer leg bones do not interfere with some other limiting physiological process. Lions may prey chiefly on old or injured zebras likely in any case to die soon, and it is not even clear that it is speed that limits the ability of lions to catch zebras.

> Greater speed may cost the zebra something in feeding efficiency, and if food rather than predation is limiting, a net selective disadvantage might result from solving the wrong problem. Finally, a longer bone might break more easily, or require greater developmental resources and metabolic energy to produce and maintain, or change the efficiency of the contraction of the attached muscles.[15]

Lewontin was not the only central figure in evolutionary biology who long ago recognized the difficulty of assessing the fitness, or adaptive value, of traits. In 1953, the paleontologist George Gaylord Simpson opined that "the fallibility of personal judgment as to the adaptive value of particular characters, most especially when these occur in animals quite unlike any now living, is notorious."[16] And in 1975, the geneticist Theodosius Dobzhansky wrote that no biologist "can judge reliably which 'characters' are useful, neutral, or harmful in a given species."[17]

One evident reason for this pessimism is that we cannot isolate traits—or the mutations producing them—as if they were independent causal elements. Organism-environment relations present us with so much complexity, so many possible parameters to track, that, apart from obviously disabling cases, there is no way to pronounce on *the* significance of a mutation for an organism, let alone for a population or for the future of the species. To pose just one question within the sea of unknowns: even if a mutation could in one way or another be deemed harmful to the organism in its current environment, what if the organism used this element of disharmony as a spur either to reshape its environment or to alter its own behavior, thereby creating a distinctive and advantageous niche for itself and others of its kind?

To see the frailty of the fitness concept most clearly, look at actual attempts to explain why a given trait renders an animal more (or less) fit in its environment. For example, many biologists have commented on the giraffe's long neck. A prominent theory, from Darwin on, has been that, in times of drought, a longer neck enabled the giraffe to browse nearer the tops of trees, beyond the reach of other animals. So any heritable changes leading to a longer neck were favored by natural selection, rendering the animal more fit and better able to survive during drought.

It sounds eminently reasonable, as such stories usually do. Problems arise only when we try to find evidence favoring this hypothesis over others. My colleague Craig Holdrege has summarized what he and others have found, including this: First, taller, longer-necked giraffes, being also heavier than their shorter ancestors, require more food, which counters

the advantage of height. Second, the many browsing and grazing antelope species did not go extinct during droughts, "so even without growing taller the giraffe ancestor could have competed on even terms for those lower leaves." Third, male giraffes are up to a meter taller than females. If the males would be disadvantaged by an inability to reach higher branches of the trees, why are not the females and young disadvantaged? Fourth, it turns out that females often feed "at belly height or below." And in well-studied populations of east Africa, giraffes often feed at or below shoulder level during the dry season, while the rainy season sees them feeding from the higher branches—a seasonal pattern the exact opposite of the one suggested by the above hypothesis.[18]

Another problem with the usual sort of fitness theorizing becomes evident when you consider the unity of the organism and the multifunctionality of its parts. Holdrege remarks of the elephant that it "stands sometimes on its back legs and extends its trunk to reach high limbs—but no one thinks that the elephant developed its trunk as a result of selection pressures to reach higher food." The trunk develops within a complex, multifaceted, interwoven unity. It "belongs" to that unity, not to a single isolated function. The effort to analyze out of this unity a particular trait and assign it a separate causal fitness is always artificial. This is certainly true of the giraffe, whose long neck not only allows feeding from high branches, but also raises the head to where the animal has the protection of a large field of view (the giraffe's vision is much more developed than its sense of smell), serves as an "arm" for the use of the head as a "club" in battles between males, and plays a vital role as a kind of pendulum enabling the animal's graceful galloping movement across the African plain.

The unworkability of the fitness concept has been widely acknowledged. Here is a summary statement of some of the problems:

> • The effect of any given mutation depends on the genetic background—the overall genetic constitution, or *genotype*—of the organism. So what a given mutation means will change as all the rest of the genome goes through its changes. How, then, do we establish *the* value of any particular mutation—and, absent any such ability, how do we make a claim of randomness?
>
> • The fitness value of any given genetic feature or combination of features can also vary with different environments. Further, "the developmental responses of different genotypes to varying environments are non-linear.... No genotype gives a phenotype

unconditionally larger, smaller, faster, slower, more or less different than another."[19]

- The fitness of a trait can, in many ways, depend on its frequency in a population. For example, predators may tend to concentrate on the more common specimens of prey while ignoring the more unusual ones, thereby giving the latter an advantage. How the resulting selection works in this sort of case "is affected by prey density, palatability, coloration and conspicuousness," and when the prey density is very high, the effect may be reversed, with predators preferentially removing rare prey.[20] Moreover, "most selective processes are frequency-dependent," notes Lewontin. As a result, the usual practice of measuring the reproductive success of organisms with particular genotypes in particular environments tells us little, if anything; but "on the other hand, it is hopeless to measure the net fitnesses of many genotypes in an immense array of different frequency combinations."[21]

- By all accounts, *reductions* in fitness can occur at various points along an evolutionary lineage—and can be essential turns in the pathway toward eventual "higher fitness." How, then, do we evaluate supposedly harmful mutations at the time we observe them, without knowing the further trajectory of the lineage?

- Perhaps most fundamentally, organisms and environments are at every moment *reciprocally* influencing each other. Organisms change their environment, and at the same time this changing environment affects the fitness of the organism's traits. When beavers dam a stream, they change their environment greatly, and at the same time the deeper, quieter water differs from swift-flowing water in the significance it gives to the beavers' swimming capacities, to their relations with predators, and so on. So the trait we are trying to assess in terms of its fitness in the existing environment is being given a different significance by an environment that is itself being altered by the trait. Where do we begin our analysis?

In Lewontin's summary: "What is required is an experimental program of unpacking 'fitness.' This involves determining experimentally how different genotypes juxtapose different aspects of the external world, how they alter that world and how those different environments that they construct affect their own biological processes and the biological processes of others."[22] I doubt whether anyone has even pretended to do this

unpacking in a way adequate to demonstrate the randomness of mutations relative to fitness.

Fitness—An Irretrievably Obscure Concept

If reduced fitness can be on the path toward higher fitness, and if the environment for which the organism is supposed to be fit is itself a modifier of the organism's fitness, then to what solid and stable ground do we anchor our idea of fitness? If asked for a definition of "fitness," most biologists, especially those who are not philosophically inclined, would probably answer with Carmen Sapienza, a professor at Temple University's Fels Institute for Cancer Research and Molecular Biology: "At bottom line, fitness is simply the number of offspring provided to the next generation."[23] And on that conviction there hangs a tale.

Along with his anecdote about the wolf, Bethell argued that evolutionary theory based on natural selection (survival of the fittest) is vacuous: it states that, first, evolution can be explained by the fact that, on the whole, only the fitter organisms survive and achieve reproductive success; and second, what makes an organism fit is the fact that it survives and successfully reproduces. This is the long-running and much-debated claim that natural selection, as an *explanation* of the evolutionary origin of species, is tautological—it cannot be falsified because it attempts no real explanation. It tells us: the kinds of organisms that survive and reproduce are the kinds of organisms that survive and reproduce.

It happens that Bethell was savaged by Stephen Jay Gould in 1976 for making this claim. Gould pointed out that Darwin and his successors hypothesized independent conditions—"engineering criteria," as biologists like to say—for the assessment of fitness.[24] These conditions may facilitate and explain reproductive success, but do not merely equate to it. In other words, the concept of fitness need not rely only on the concept of survival (or reproductive success).

However, the appeal to engineering criteria in the abstract does not by itself get us very far. As philosopher Ronald Brady reminded us when discussing this dispute in an essay entitled "Dogma and Doubt," what matters for judging a proposed scientific explanation is not only the specification of non-tautological criteria for testing it, but also our ability to apply the test meaningfully.[25] If we have no practical way to sum up and assess the fitness or adaptive value of the traits of an organism apart from measurements of survival rates (evolutionary success), then on what basis can we use the idea of survival of the fittest (natural selection) to *explain*

evolutionary success—as opposed to using it merely as a blank check for freely inventing explanations of the sort commonly derided as "just-so stories."

Some philosophers and evolutionary biologists have long referred with a note of patronizing scorn to anyone who brings up the "tautology problem," as if the reference betrays hopeless ignorance of a problem long ago solved. For example, Michael Ruse, reviewing a book by Philip Kitcher, could already refer in 1984 to the "hoary old chestnut" about tautology, and then (in sympathy with Kitcher) dismiss the claim as "ridiculous." After all, he writes, "Could generations of evolutionists really have been deceived into thinking they were doing empirical studies, when they spent hours crouched over fruit-flies in the lab, or weeks tramping through the woods looking at butterflies, snails, and finches? A tautology requires no such study."[26]

But what is really ridiculous is to suggest that empirical work, simply by virtue of being empirical work, offers a proper test of any particular theory. Certainly the work of evolutionary biologists has brought us many wonderful insights into the lives of organisms—insights of the sort that were being gained long before Darwin. But such insights provide a test of the theory that the origin of species can be adequately explained by natural selection of the fittest organisms only if they do in fact provide a test. Simply refusing to address the question does no one any good. (The dismissive attitude exemplified by Ruse continues into our own day. As a response to it, Brady's essays remain relevant and illuminating.)

But for our purposes, the argument about tautology is of interest not so much as an issue in itself (I build no case on it), but because all the sound and fury that have been vented over the topic point us toward the obscurity dogging all discussions of fitness. It is no minor problem. You have to have *some* reasonable notion of "fitness" if you are trying to explain all the amazingly complex, well-adapted, and diverse life forms on earth by the fact that nature preferentially selects the fitter organisms to survive. The question, "What, exactly, is being selected, and how does it explain the observed course of evolution?" needs to be answered if the theory of evolution by natural selection is to be much of a theory at all.

To make the problem worse, evolutionary biologists are driven to arrive at scalar values for fitness—values enabling reasonable comparison of traits and organisms, so that we can determine which is the fittest. But how do you take all the infinitely wide-ranging and interwoven considerations that might bear on fitness and reduce them to a scalar value? It is a practical impossibility. As a pair of philosophers put it in a 2002

article, "Suppose a certain species undertakes parental care, is resistant to malaria, and is somewhat weak but very quick. How do these fitness factors add up? We have no idea at all."[27]

Susan K. Mills and John H. Beatty, major contributors to the most popular theory of fitness (a now rather shopworn and probabilistic theory known as the *propensity theory*), acknowledge that "since an organism's traits are obviously important in determining its fitness, it is tempting to suggest that fitness be defined independently of survival and reproduction, as some function of traits"—that is, presumably, in terms of engineering criteria. Noting that such a definition would have the advantage of being noncircular, they go on:

> However, no one has seriously proposed such a definition, and it is easy to see why. The features of organisms which contribute to their survival and reproductive success are endlessly varied and context dependent. What do the fittest germ, the fittest geranium, and the fittest chimpanzee have in common? It cannot be any concretely characterized physical property, given that one and the same physical trait can be helpful in one environment and harmful in another.[28]

More than a decade later, Beatty remarked that "the precise meaning of 'fitness' has yet to be settled, in spite of the fact—or perhaps because of the fact—that the term is so central to evolutionary thought."[29] This is, if anything, even more emphatically true today. The concept remains troubled, as it has been from the very beginning, with little agreement on how to make it a workable part of evolutionary theory. Indeed, the "consensus view," as Roberta L. Millstein and Robert A. Skipper, Jr., write in *The Cambridge Companion to the Philosophy of Biology*, is that "biologists and philosophers have yet to provide an adequate interpretation of fitness."[30] And Lewontin, together with University of Missouri philosopher André Ariew, expresses the conviction that "no concept in evolutionary biology has been more confusing" than that of fitness.[31] Yet the neo-Darwinian theory of natural selection hinges, in its "status…as empirical science," upon a reasonable understanding of what fitness means.[32]

'Couldn't You Be More Explicit Here?'

This is a stunning place to find ourselves, given the confident pronouncements we heard issuing from Dennett and Dawkins at the outset of our investigation. Not only do we have great difficulty locating meaningless chance in the context of the actual life of organisms; it now turns out that

the one outcome with respect to which randomness of mutation is supposed to obtain—namely, the organism's fitness—cannot be given any definite or agreed-upon meaning, let alone one that is testable. How then did anyone ever arrive at the conclusion that mutations are random in relation to fitness? There certainly has never been any empirical demonstration of the conclusion, and it is difficult even to conceive the possibility of such a demonstration.

What we are left to surmise, then, is that the doctrine of randomness has simply been projected onto the phenomena of organic life as a matter of pre-existing philosophical commitment.

In any case, it is startling to realize that the entire brief for demoting human beings, and organisms in general, to meaningless scraps of molecular machinery—a demotion that fuels the long-running science-religion wars and that, as "shocking" revelation, supposedly stands on a par with Copernicus's heliocentric proposal—rests on the vague conjunction of two scarcely creditable concepts: the randomness of mutations and the fitness of organisms. And, strangely, this shocking revelation has been sold to us in the context of a descriptive biological literature that, from the molecular level on up, remains almost *nothing but* a documentation of the meaningfully organized, goal-directed stories of living creatures.

Here, then, is what the advocates of evolutionary mindlessness and meaninglessness would have us overlook. We must overlook, first of all, the fact that organisms are masterful participants in, and revisers of, their own genomes, taking a leading position in the most intricate, subtle, and intentional genomic "dance" one could possibly imagine. And then we must overlook the way the organism responds intelligently, and in accord with its own purposes, to whatever it encounters in its environment, including the environment of its own body, and including what we may prefer to view as "accidents." Then, too, we are asked to ignore not only the living, reproducing creatures whose intensely *directed* lives provide the only basis we have ever known for the dynamic processes of evolution, but also all the meaning of the larger environment in which these creatures participate—an environment compounded of all the infinitely complex ecological interactions that play out in significant balances, imbalances, competition, cooperation, symbioses, and all the rest, yielding the marvelously varied and interwoven *living communities* we find in savannah and rainforest, desert and meadow, stream and ocean, mountain and valley. And then, finally, we must be sure to pay no heed to the fact that the fitness, against which we have assumed our notion of randomness could be defined, is one of the most obscure, ill-formed concepts in all of science.

Overlooking all this, we are supposed to see—*somewhere*—blind, mindless, random, purposeless automatisms at the ultimate explanatory root of all genetic variation leading to evolutionary change.

The situation calls to mind a widely circulated cartoon by Sidney Harris, which shows two scientists in front of a blackboard on which a body of theory has been traced out with the usual tangle of symbols, arrows, equations, and so on. But there's a gap in the reasoning at one point, filled by the words, "Then a miracle occurs." And the one scientist is saying to the other, "I think you should be more explicit here in step two."

In the case of evolution, I picture Dennett and Dawkins filling the blackboard with their vivid descriptions of living, highly regulated, coordinated, integrated, and intensely meaningful biological processes, and then inserting a small, mysterious gap in the middle, along with the words, "Here something random occurs."

This "something random" looks every bit as wishful as the appeal to a miracle. It is the central miracle in a gospel of meaninglessness, a "Randomness of the gaps," demanding an extraordinarily blind faith. At the very least, we have a right to ask, "Can you be a little more explicit here?" A faith that fills the ever-shrinking gaps in our knowledge of the organism with a potent meaninglessness capable of transforming everything else into an illusion is a faith that could benefit from some minimal grounding. Otherwise, we can hardly avoid suspecting that the importance of randomness in the minds of the faithful is due to its being the only presumed scrap of a weapon in a compulsive struggle to deny all the obvious meaning of our lives.

Supplement: Natural Genome Remodeling

In her 1983 Nobel address, geneticist Barbara McClintock cited various ways an organism responds to stress by, among other things, altering its own genome. "Some sensing mechanism must be present in these instances to alert the cell to imminent danger," she said, adding that "a goal for the future would be to determine the extent of knowledge the cell has of itself, and how it utilizes this knowledge in a 'thoughtful' manner when challenged."[33] Subsequent research has shown how far-seeing she was.

It is now indisputable that genomic change of all sorts is rooted in the remarkable "expertise" of the organism as a whole. By means of endlessly complex and interweaving processes, the organism sees

to the replication of chromosomes in dividing cells, maintains surveillance for all sorts of damage, and repairs or alters damage when it occurs—all with an intricacy and subtlety of well-gauged action that far exceeds, at the molecular level, what the most skillful surgeon accomplishes at the tissue level. But it's not just a matter of preserving a fixed DNA sequence. In certain human immune-system cells, portions of DNA are repeatedly cut and then stitched together in new patterns, yielding the huge variety of proteins required for recognizing an equally huge variety of foreign substances that need to be rendered harmless. Clearly, our bodies have gained the skills for elaborate reworking of their DNA—and, we will see further, in many different ways.

Depending on stage of development, cell type, and state of health, among other things, our cells convert millions of their genomic "letters" (most often the letter C, standing for the cytosine base) to an altered letter in a process known as "DNA methylation." The new letter, 5-methylcytosine, is often referred to as the "fifth base" of the genome, and it has profound implications for gene expression that are far too extensive to survey here. The organism also contrives to effect several other kinds of DNA letter changes. The DNA sequence, it turns out, is subject to intense revision through its participation in the life of the larger whole.

More emphatically, and with remarkable nuance, the organism contextualizes its genome, and it makes no sense to say that these powers of contextualization are under the control of the genome being contextualized. Thus, the human genome yields itself to a radical and stable "redefinition" of its meaning in the extremely varied environments of some 250 different cell types (and thousands of subtypes) found in brain and muscle, liver and skin, blood and retina. It is well to remember that the genes in your stomach lining and the genes in the cornea of your eye are supposed to be the "same" genes, and yet the immediate context makes very different things out of them. An especially revealing case of contextualization occurs when a genome fit for the needs of all the varied cells of a worm-like larva is subsequently pressed into perfectly adequate service for the entirely different cell types—and different bodily organization and different overall functioning—of a graceful, airborne butterfly. The genome, it appears, is to one extent or another like clay that can be molded in

many different ways by the organism as a whole, according to contextual need.

Jumping for Change. Quite aside from such contextualization, it has long been known that the organism generates altogether new genetic material by duplicating entire genes, modifying them, and supplying them with regulatory elements. This can occur through direct duplication of genes or even larger chromosomal segments, and also through reverse transcription, whereby messenger RNA molecules, produced from DNA, are transcribed back into new DNA, which can then be modified. But "the array of mechanisms underlying the origin of new genes is compelling, extending way beyond the traditionally well-studied source of gene duplication," writes Henrik Kaessmann of the Center for Integrative Genomics in Switzerland.[34]

In a broad overview of the relevant studies, Kaessmann documents a dizzying variety of techniques by which the organism diversifies and enlarges its genetic repertoire. For example, two duplicated genes can, via a number of different pathways, fuse into a single *chimeric* gene. And not only protein-coding RNAs, but also small regulatory RNAs can be reverse-transcribed into DNA and their functions diversified. And again, various repetitive and mobile elements called "transposons" can move around in the genome, often being duplicated in the process and then co-opted either as new protein-coding genes or new regulatory genes.[35]

Let's pause for a moment to look a little more closely at these transposons. "It now is undeniable," writes a team of researchers from the United States, Canada, Spain, and the United Kingdom, "that transposable elements, historically dismissed as junk DNA, have had an instrumental role in sculpting the structure and function of our genomes."[36] Directly and indirectly, transposable elements are being found crucial to many aspects of genome organization and renovation. And the diverse means by which the cell employs and regulates them have only begun to be delineated.

These transposons, also known as "jumping genes" (whose discovery led to Barbara McClintock's Nobel prize), may hold the key to a puzzle about inbred mice. Such mice, with their perfectly matched genes, are sometimes reared in the laboratory under the strictest and most identical conditions possible. The frustration for researchers,

according to Fred Gage, a neuroscientist at the Salk Institute for Biological Studies in San Diego, is that "you control for everything you can, and in behavioral tests, the variance is enormous." Even within a single litter, "one mouse will be unusually smart, another below average." Gage and others are proposing that jumping genes help account for this otherwise mysterious diversity.[37]

Whatever may be going on with the mice, it has now been shown that transposons move around in the developing mammalian brain, altering the genome from cell to cell. They provide enough diversity among neurons, according to Gage, so that "you can optimize your response to the variety of environments you might encounter throughout life." And now it is being found that transposons also "jump" in other cell types much more readily than was previously thought. This particularly includes various cells of the early embryo, in which case each genetically altered cell propagates its changes into a subset of the mature organism's tissues, making them genetically distinct from other tissues. "Given how often this may happen in the early embryo, there may be much more genomic variation within individuals than most researchers had assumed," writes one reporter in *Science*.[38]

None of this looks particularly haphazard. In embryonic stem cells the regulatory DNA elements known as *enhancers* of gene expression contain an elevated number of transposons. And germ cells (of which I will have more to say in a moment) are also especially susceptible to these mutable, or mobile, elements.[39] The cell-type-specific and DNA-element-specific nature of transposon activity points to a meaningfully orchestrated process. In general, there is a bias for many transposable elements to insert themselves upstream of transcription start sites, which "prevents damage to functional coding elements and enhances the potential for a constructive regulatory change."[40]

Are transposons mere parasites? An extraordinarily profound role for jumping genes has just recently come to light with the announcement by Yale University researchers that the evolution of placental development (and hence prolonged pregnancy) in mammals was intimately bound up with the regulatory role of transposons. The Yale team found that a network of 1,532 genes recruited for expression in the human uterus (but not in marsupials, a mammalian group whose members give birth to undeveloped young a mere two weeks after

conception) is coordinated by transposons. "We used to believe that changes only took place through small mutations in our DNA that accumulated over time," remarked the lead researcher in the project, Günter Wagner. "But in this case we found a huge cut-and-paste operation that altered wide areas of the genome to create large-scale morphological change."[41]

The study authors say that their findings "strongly support the existence of transposon-mediated gene regulatory innovation at the network level, a mechanism of gene regulation first suggested more than forty years ago by McClintock.... Transposable elements are potent agents of gene regulatory network evolution."[42]

It is no wonder, then, that when genomic researcher David Haussler of the University of California, Santa Cruz was asked by the journal *Cell* what has been most surprising about the human genome, one of the things he cited was "mounting evidence" that transposons "play a critical role" in the turnover and reinvention of regulatory elements in DNA.[43] And, responding in *Science* to a report about the work on jumping genes in mammalian brains, Southern Illinois University neuroscientist David G. King wrote that the "dismissive dictum, 'Mutations are accidents,' has grown obsolete," adding that protocols for "the spontaneous, non-accidental production of genetic variation are deeply embedded in genomic architecture."[44]

One other remark about transposons: They exemplify a growing (and, for biologists, embarrassing) class of cellular constituents that were initially dismissed as more or less functionless simply because they didn't fit into a kind of neat (but now hopelessly outmoded) digital coding schema linking DNA as Master Cause, to RNA as precisely programmed mediary, to protein as definitive final result. Making up a sizable portion of the human genome, transposons are to this day often referred to as "junk" or "parasitic" elements. Because they play a particularly prominent (and still barely explored) role in the germline, one often hears about the germ cell's "defensive mechanisms" to protect itself from these highly mobile, "selfish" elements, with their genome restructuring potentials. How this kind of thinking could go on for many years without most biologists suspecting a positive role for transposons as genome remodelers with potentially powerful implications for evolution is a great mystery. Certainly transposons, like everything else in the cell, are subject to intense oversight by their larger

context—and viruses may indeed have played a role in their origin, as many suppose—but this hardly makes them mere parasites in the organisms that have so intently taken them up and put them to use.

Out of thin air? With transposons, the organism reshapes its genome through elaborately organized and synchronized processes often affecting considerable stretches of DNA. But even more striking, Kaessmann notes, is the recent discovery of protein-coding genes being composed "from scratch"—that is, from non-protein-coding genomic sequences altogether unrelated to pre-existing genes or transposable sequences. He cites a famous 1977 paper by the preeminent French biologist François Jacob to the effect that the probability for creation of new protein-coding genes *de novo* (from scratch) by random processes "is practically zero."[45] Such creation was widely thought to be virtually impossible. And yet, Kaessmann goes on, "recent work has uncovered a number of new protein-coding genes that apparently arose from previously noncoding (and nonrepetitive) DNA sequences."

If we take seriously Jacob's "practically zero" probability for random, *de novo* assembly of functional, protein-coding genes from noncoding DNA sequences, then, given that such assembly does in fact somehow occur, the obvious thing to suspect is that the process is not random. Nor does the scale of the problem, as it is now emerging, look trivial. There is, we're told by two biologists working in Germany—one at the Max Planck Institute for Evolutionary Biology and one at Christian Albrechts University—"accumulating evidence that *de novo* evolution of genes from noncoding sequences could have an important role" in a class of genes representing "up to one-third of the genes in all genomes."[46] The seemingly unbridgeable gap between "practically zero" and this recent extraordinary claim invites evolutionary geneticists to do a lot of soul-searching.

Concerted change in the germline. There is nothing in the picture so far to suggest that, when turning our attention to genetic change in reproduction, we will find much evidence of randomness. Everything we've looked at so far occurs in germline cells as well. But in these cells we witness additional powers of change that could hardly be exceeded. Nowhere, for example, do we see the genome more concertedly reshaped than in the two meiotic cell divisions leading to the formation

of gametes in sexual reproduction—a choreography we hear described in the accompanying main article as the "meiotic ballet."

One of the central features of this ballet, referred to as "chromosomal crossover" or "genetic recombination," involves an insistent reshuffling of stretches of DNA between chromosomes, resulting in genetic variation in the offspring. You could hardly imagine a more carefully and delicately staged dance than the one resulting in chromosomal crossover—and, with researchers speaking of "recombination hotspots" and all sorts of regulation, we can be sure it is not at all random. As usual in the cell, many different factors within the larger whole come to bear on any specific point:

> As is the case for transcription, no single type of DNA site, transcription factor, or histone modification can account for the regulated positioning of all recombination. Instead, these elements function combinatorially (with potential for synergism, antagonism and redundancy) to establish preferential sites of action by meiotic recombination protein complexes.[47]

Context, as always, figures strongly (and nonrandomly) in shaping and directing local activities.

Kaessmann further points to studies in animals showing that the testes play a "potentially central role in the process of gene birth and evolution." For example, there is an "overall propensity" of young retrogenes—genes copied back into DNA by reverse transcription from RNA—to be expressed in the testes. "The testis may represent a crucible for new gene evolution, allowing novel genes to form and evolve, and potentially adopt functions in other (somatic) tissues with time."

Likewise, pluripotent cells such as stem cells, which bear certain similarities to germline cells, possess genomes that are "amazingly plastic": "The incredible plasticity of pluripotent genomes is a notable discovery, and reveals the view of an unexpectedly dynamic mammalian genome for many of us."[48]

Powers of change converging from all sides. In sum, as Kaessmann writes, recent work in genomics has laid bare

> an astounding diversity of mechanisms underlying the birth of more recent genes. Almost any imaginable pathway toward new gene birth seems to have been documented by now, even those

> previously deemed highly unlikely or impossible. Thus, new genes have arisen from copies of old ones, protein and RNA genes were composed from scratch, protein-coding genes metamorphosed into RNA genes, parasitic genome sequences were domesticated, and, finally, all of the resulting components also readily mixed to yield new chimeric genes with unprecedented functions.[49]

None of this is yet to mention the way the organism massively structures, restructures, and regulates its genome through the intricate remodeling of chromatin (the DNA/protein/RNA complex comprising our chromosomes), or the way it shapes the dynamic, three-dimensional organization of the cell nucleus, which in turn has a great deal to do with how genes get expressed. (See the first article in this set, "Getting Over the Code Delusion" [Summer 2010].) Even regarding the bare DNA sequence in the narrowest sense, Italian geneticist Vittorio Sgaramella, after noting the various alterations of the sequence throughout the cells of our bodies, was led to ask, "Which is our real genome…?" He adds, "The human genome seems more complex but less autonomous than originally believed."[50] Less autonomous because so many concerted activities of the organism are brought to bear on it.

And there is still much more we could have spoken about. For example, there is a consensus today that entire organelles of the cell originated in evolutionary history through a kind of cooperative fusion of distinct microorganisms, a process requiring an almost unimaginable degree of intricate coordination among previously independent life processes. There is also the well-demonstrated reality of lateral gene transfer, which looks like invalidating the image of an evolutionary "tree," especially at the level of simpler organisms: repeated horizontal exchanges of genetic material between distinct species make large portions of the tree look more like a complex web. Then, again, there is good evidence that viruses have played a major role in contributing to the genomes of more complex organisms, including mammals and humans. In all this, we find organisms bringing their separate, highly coordinated life processes to bear upon each other in a symbiotic or other interactive manner that can no more be described as "random" than can, say, the complex and elaborately orchestrated mating processes we see among sexually reproducing organisms.

Then, too, we could have looked at convergent evolution and the way it commonly involves changes to corresponding genes in widely

different organisms, which "implies a surprising predictability underlying the genetic basis of evolutionary changes."[51] And there is the rapidly rising interest in a kind of neo-Lamarckian, epigenetically mediated inheritance of acquired characteristics. But we have already seen enough to realize that, by one means or another, the organism pursues its own genomic alterations with remarkable insistence and subtlety.

Where is randomness? All these revelations about coherent genomic change have prompted University of Chicago geneticist James A. Shapiro to speak of "natural genetic engineering." "We have progressed from the Constant Genome, subject only to random, localized changes at a more or less constant mutation rate, to the Fluid Genome, subject to episodic, massive and non-random reorganizations capable of producing new functional architectures."[52] Crucially, "genetic change is almost always the result of cellular action on the genome."[53]

Likewise, two geneticists from the University of Michigan Medical School, writing in *Nature Reviews Genetics*, remember how "it was previously thought that most genomic rearrangements formed randomly." Now, however, "emerging data suggest that many are non-random, cell type-, cell stage- and locus-specific events. Recent studies have revealed novel cellular mechanisms and environmental cues that influence genomic rearrangements."[54]

Bear in mind that we've been looking at the one aspect of organismal functioning—the mutational aspect—where we are assured most confidently that "blind chance," or randomness, becomes visible within the evolutionary process. Certainly *from the organism's side* we see nothing to suggest any fundamental role for randomness. The accompanying article explores the question in a larger context, where our understanding of evolutionary *fitness* becomes crucial.

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