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More Articles on Evolution

A Third Way

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The recent reviews in your columns of books by Dennett, Dawkins, and Behe are testimony to the unflagging interest in controversies about evolution. Although such purists as Dennett and Dawkins repeatedly assert that the scientific issues surrounding evolution are basically solved by conventional neo-Darwinism, the ongoing public fascination reveals a deeper wisdom. There are far more unresolved questions than answers about evolutionary processes, and contemporary science continues to provide us with new conceptual possibilities.

Unfortunately, readers of *Boston Review* may remain unaware of this intellectual ferment because the debate about evolution continues to assume the quality of an abstract and philosophical "dialogue of the deaf" between Creationists and Darwinists. Although our knowledge of the molecular details of biological organization is undergoing a revolutionary expansion, open-minded discussions of the impact of these discoveries are all too rare. The possibility of a non-Darwinian, scientific theory of evolution is virtually never considered. In my comments, then, I propose to sketch some developments in contemporary life science that suggest shortcomings in orthodox evolutionary theory and open the door to very different ways of formulating questions about the evolutionary process. After a discussion of technical advances in our views about genome organization and the mechanisms of genetic change, I will focus on a growing convergence between biology and information science which offers the potential for scientific investigation of possible intelligent cellular action in evolution.

The past five decades of research in genetics and molecular biology have brought us revolutionary discoveries. Upsetting the oversimplified views of cellular organization and function held at mid-century, the molecular revolution has revealed an unanticipated realm of complexity and interaction more consistent with computer technology than with the mechanical viewpoint which dominated the field when the neo-Darwinian Modern Synthesis was formulated. The conceptual changes in biology are comparable in magnitude to the transition from classical physics to relativistic and quantum physics.

Four categories of molecular discoveries are especially important in opening up exciting new ways of thinking about the biological processes that underlie evolutionary change.

(1) *Genome Organization*. Our current ideas of genome organization are completely different from the "beads on a string" view that dominated genetics in the 1940s and 1950s. At that time genes were "units" which corresponded to individual organismal traits, and the "one gene-one enzyme" hypothesis told us that the essential business of each gene was to encode a specific protein molecule linked to a particular phenotype. We have now deconstructed each genetic locus into a modular assembly of regulatory and coding motifs. Most of these motifs are shared among many loci, suggesting that genomes are assembled Lego-like from a repertoire of more basic sequence elements, many of which do not encode proteins but determine other important functions (transcription, translation, RNA processing, DNA replication, chromatin condensation, etc.). As we analyze genome expression during cellular proliferation and

multicellular development, we have learned that diverse genetic loci are organized hierarchically into interconnected genome-wide networks which function dynamically. Not confined to a single pathway, many genetic loci are active at different times, participating in the expression of more than one phenotypic trait. Comparisons of genomes in different organisms have revealed unexpected patterns of evolutionary conservation across large taxonomic distances, while closely-related genomes frequently differ significantly in the arrangement of repetitive DNA elements which do not encode proteins.

How all of this modularity, complexity, and integration arose and changed during the history of life on earth is a central evolutionary question. Localized random mutation, selection operating "one gene at a time" (John Maynard Smith's formulation), and gradual modification of individual functions are unable to provide satisfactory explanations for the molecular data, no matter how much time for change is assumed. There are simply too many potential degrees of freedom for random variability and too many interconnections to account for.

Studies of the molecular sources of genetic variability have taught us two major lessons about how cells take care of their genomes--one about self-protection, the other about self-reorganization.

(2) *Cellular Repair Capabilities*. First, then, all cells from bacteria to man possess a truly astonishing array of repair systems which serve to remove accidental and stochastic sources of mutation. Multiple levels of proofreading mechanisms recognize and remove errors that inevitably occur during DNA replication. These proofreading systems are capable of distinguishing between newly synthesized and parental strands of the DNA double helix, so they operate efficiently to rectify rather than fix the results of accidental misincorporations of the wrong nucleotide. Other systems scan non-replicating DNA for chemical changes that could lead to miscoding and remove modified nucleotides, while additional functions monitor the pools of precursors and remove potentially mutagenic contaminants. In anticipation of chemical and physical insults to the genome, such as alkylating agents and ultraviolet radiation, additional repair systems are encoded in the genome and can be induced to correct damage when it occurs.

It has been a surprise to learn how thoroughly cells protect themselves against precisely the kinds of accidental genetic change that, according to conventional theory, are the sources of evolutionary variability. By virtue of their proofreading and repair systems, living cells are not passive victims of the random forces of chemistry and physics. They devote large resources to suppressing random genetic variation and have the capacity to set the level of background localized mutability by adjusting the activity of their repair systems.

(3) *Mobile Genetic Elements and Natural Genetic Engineering*. The second major lesson of molecular studies into the origins of genetic change is that all cells possess multiple biochemical agents for natural genetic engineering--processes that include the cutting and splicing of DNA molecules into new sequence arrangements. Most frequently, natural genetic engineering capabilities reveal themselves through the activities of mobile genetic elements--DNA structures found in all genomes that can move from one position to another. Mobile genetic elements are the most fluid components of the genome and also the most taxonomically specific. In human cells, mobile elements include retrotransposons, like the half-million or more Alu sequences dispersed over all our chromosomes, as well as the inherited gene fragments which our lymphocytes assemble daily to form active genetic loci encoding the key antigen recognition molecules of our immune system. The biochemical agents of DNA restructuring include the enzymes used in our own genetic engineering for research and biotechnology (nucleases, ligases, reverse transcriptases and polymerases) as well as other proteins that combine to form molecular machines capable of mobilizing different genomic components.

The existence of cellular biochemical activities capable of rearranging DNA molecules means

that genetic change can be specific (these activities can recognize particular sequence motifs) and need not be limited to one genetic locus (the same activity can operate at multiple sites in the genome). In other words, genetic change can be massive and non-random. Some organisms, such as the ciliated protozooan Oxytricha, completely reorganize their genetic apparatus within a single cell generation, fragmenting the germ-line chromosomes into thousands of pieces and then reassembling a particular subset of them into a distinct kind of functional genome. Furthermore, natural genetic engineering systems can operate premeiotically during the somatic development of tissues that will ultimately produce gametes. This means that major chromosome reorganizations can be present in multiple gametes. Consequently, the appearance of new genome architectures during evolution is not necessarily limited to isolated individuals.

The discovery that genome reorganization is largely a biological process traces back to Barbara McClintock's pioneering studies of mutation and chromosome rearrangement in maize from the 1940s through the 1960s. She linked these genetic events to changes in the regulation of gene expression programs during plant development. We can now appreciate her tremendous wisdom and foresight by seeing how the Lego-like patterns of integrated genome organization mentioned above could be created by the activity of cellular natural genetic engineering systems. Because, like all cellular functions, natural genetic engineering systems are subject to control circuits, they can be held in abeyance for long periods and then called into action at certain key times. Sometimes these activations can be regularly programmed, as in the development of our immune systems, and sometimes activations can occur in response to crisis, as McClintock documented in maize.

The point of this discussion is that our current knowledge of genetic change is fundamentally at variance with neo-Darwinist postulates. 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. Inevitably, such a profound advance in awareness of genetic capabilities will dramatically alter our understanding of the evolutionary process. Nonetheless, neo-Darwinist writers like Dawkins continue to ignore or trivialize the new knowledge and insist on gradualism as the only path for evolutionary change.

(4) *Cellular Information Processing*. While it is easy to see how advances in our understanding of genome organization and genetic change will impact theories of evolutionary processes, another development in contemporary biology is of less obvious but even more basic relevance. This is the growing realization that cells have molecular computing networks which process information about internal operations and about the external environment to make decisions controlling growth, movement, and differentiation. This realization has come, in large measure, from detailed genetic analysis of cellular processes and multicellular development. The inducible repair systems mentioned above provide a relatively simple, well-studied example. Bacterial and yeast cells have molecules that monitor the status of the genome and activate cellular responses when damaged DNA accumulates. The surveillance molecules do this by modifying transcription factors so that appropriate repair functions are synthesized. These inducible DNA damage response systems are sophisticated and include so-called "checkpoint" functions that act to arrest cell division until the repair process has been completed. When the checkpoints do not function, cell division proceeds before repair is completed, and the damaged cells die or produce inviable progeny. One can characterize this surveillance/inducible repair/checkpoint system as a molecular computation network demonstrating biologically useful properties of self-awareness and decision-making.

There are many other cellular systems that display comparable information-processing capabilities. Fro example, it is now common among molecular biologists who study the cell cycle to speak of various checkpoints (Is DNA replication complete? Are the chromosomes properly condensed and aligned on the metaphase plate?) and decision points (e.g., when to

initiate chromosome movement and cytokinesis).

A recent special issue of *Scientific American*[1] describes beautifully how cancer is now seen as a disease of the molecular information processing routines that ensure orderly cell growth and behavior in the healthy organism. Aberrant tumor cell growth appears to result from at least two kinds of malfunction: the loss of checkpoint controls, or the failure of decision-making routines that dictate programmed cell death (apoptosis) for cells in inappropriate surroundings. During embryonic development, cells make decisions about differentiation based on multiple molecular signals picked up from their environment and from their neighbors by means of surface receptors. These receptors are linked to intercellular molecular cascades called "signal transduction pathways" which integrate the inputs from the receptors to generate appropriate patterns of differential gene expression and morphogenesis of specialized cell structures.

Signal transduction is not limited to multicellular development. We are learning that virtually every aspect of cellular function is influenced by chemical messages detected, transmitted, and interpreted by molecular relays. To a remarkable extent, therefore, contemporary biology has become a science of sensitivity, inter- and intra-cellular communication, and control. Given the enormous complexity of living cells and the need to coordinate literally millions of biochemical events, it would be surprising if powerful cellular capacities for information processing did not manifest themselves. In an important way, then, biology has returned to questions debated during the mechanism-vitalism controversy earlier this century. This time around, however, the discussion is informed by two new factors. One is that the techniques of molecular and cell biology allow us to examine the detailed operation of the hardware responsible for cellular responsiveness and decision-making. The second is the existence of computers and information networks, physical entities endowed with computational and decision-making capabilities. Their existence means that discussing the potential for similar activities by living organisms is neither vague nor mystical.

What significance does an emerging interface between biology and information science hold for thinking about evolution? It opens up the possibility of addressing scientifically rather than ideologically the central issue so hotly contested by fundamentalists on both sides of the Creationist-Darwinist debate: Is there any guiding intelligence at work in the origin of species displaying exquisite adaptations that range from lambda prophage repression and the Krebs cycle through the mitotic apparatus and the eye to the immune system, mimicry, and social organization? Borrowing concepts from information science, new schools of evolutionists can begin to rephrase virtually intractable global questions in terms amenable to computer modelling and experimentation. We can speculate what some of these more manageable questions might be: How can molecular control circuits be combined to direct the expression of novel traits? Do genomes display characteristic system architectures that allow us to predict phenotypic consequences when we rearrange DNA sequence components? Do signal transduction networks contribute functional information as they regulate the action of natural genetic engineering hardware?

Questions like those above will certainly prove to be naive because we are just on the threshold of a new way of thinking about living organisms and their variations. Nonetheless, these questions serve to illustrate the potential for addressing the deep issues of evolution from a radically different scientific perspective. Novel ways of looking at longstanding problems have historically been the chief motors of scientific progress. However, the potential for new science is hard to find in the Creationist-Darwinist debate. Both sides appear to have a common interest in presenting a static view of the scientific enterprise. This is to be expected from the Creationists, who naturally refuse to recognize science's remarkable record of making more and more seemingly miraculous aspects of our world comprehensible to our understanding and accessible to our technology. But the neo-Darwinian advocates claim to be scientists, and we

can legitimately expect of them a more open spirit of inquiry. Instead, they assume a defensive posture of outraged orthodoxy and assert an unassailable claim to truth, which only serves to validate the Creationists' criticism that Darwinism has become more of a faith than a science.

A sounder perspective on the history of science would be very helpful to all concerned. For example, a parallel has been drawn by Allen Orr and others between criticisms of Darwinian orthodoxy and assaults on the Law of Gravity, presenting them as equally deplorable examples of anti-science obscurantism. Yet, if truth be told, gravity is far from a settled matter. The relativistic Law of Gravity at the end of the 20th century is not the same as the classical Law of Gravity at the end of the 19th century, and discovering how the continuous descriptions of general relativity can be integrated into a single theory with the discrete accounts of quantum physics is still an active field of research. From a scientific point of view, then, the Law of Gravity has quite properly been under continuous challenge. Dogmas and taboos may be suitable for religion, but they have no place in science. No theory or viewpoint should ever become sacrosanct because experience tells us that even the most elegant Laws of Nature ultimately succumb to the inexorable progress of scientific thinking and technological innovation. The present debate over Darwinism will be more productive if it takes place in recognition of the fact that scientific advances are made not by canonizing our predecessors but by creating intellectual and technical opportunities for our successors.

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1 Robert Weinberg, "How Cancer Arises," *Scientific American* 275, no. 3 (September 1996), pp. 62-70.

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