

Unraveling the DNA Myth

The Spurious Foundation of Genetic Engineering

by Barry Commoner
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Biology once was regarded as a languid, largely descriptive discipline, a passive science that was content, for much of its history, merely to observe the natural world rather than change it. No longer. Today biology, armed with the power of genetics, has replaced physics as the activist Science of the Century and it stands poised to assume godlike powers of creation, calling forth artificial forms of life rather than undiscovered elements and sub-atomic particles. The initial steps toward this new Genesis have been widely touted in the press. It wasn't so long ago that Scottish scientists stunned the world with Dolly, the fatherless sheep cloned directly from her mother's cells: these techniques have now been applied, unsuccessfully, to human cells. ANDi, a photogenic rhesus monkey, recently was born carrying the gene of a luminescent jellyfish. Pigs now carry a gene for bovine growth hormone and show significant improvement in weight gain, feed efficiency, and reduced fat. Most soybean plants grown in the United States have been genetically engineered to survive the application of powerful herbicides. Corn plants now contain a bacterial gene that produces an insecticidal protein rendering them poisonous to earworms.

Our leading scientists and scientific entrepreneurs (two labels that are increasingly interchangeable) assure us that these feats of technological prowess, though marvelous and complex, are nonetheless safe and reliable. We are told that everything is under control. Conveniently ignored, forgotten, or in some instances simply suppressed are the caveats, the fine print, the flaws and spontaneous abortions. Most clones exhibit developmental failure before or soon after birth, and even apparently normal clones often suffer from kidney or brain malformations. ANDi, perversely, has failed to glow like a jellyfish. Genetically modified pigs have a high incidence of gastric ulcers, arthritis, cardiomegaly (enlarged heart), dermatitis, and renal disease. Despite the biotechnology industry's assurances that genetically engineered soybeans have been altered only by the presence of the alien gene, as a matter of fact the plant's own genetic system has been unwittingly altered as well, with potentially dangerous consequences. The list of malfunctions gets little notice; biotechnology companies are not in the habit of publicizing studies that question the efficacy of their miraculous products or suggest the presence of a serpent in the biotech garden.

The mistakes might be dismissed as the necessary errors that characterize scientific progress. But behind them lurks a more profound failure. The wonders of genetic science are all founded on the discovery of the DNA double helix -- by Francis Crick and James Watson in 1953 -- and they proceed from the premise that this molecular structure is the exclusive agent of inheritance in all living things: in the kingdom of molecular genetics, the DNA gene is

absolute monarch. Known to molecular biologists as the "central dogma" the premise assumes that an organism's genome -- its total complement of DNA genes -- should fully account for its characteristic assemblage of inherited traits. The premise, unhappily, is false. Tested between 1990 and 2001 in one of the largest and most highly publicized scientific undertakings of our time, the Human Genome Project, the theory collapsed under the weight of fact. There are far too few human genes to account for the complexity of our inherited traits or for the vast inherited differences between plants, say, and people. By any reasonable measure, the finding (published last February) signaled the downfall of the central dogma; it also destroyed the scientific foundation of genetic engineering, and the validity of the biotechnology industry's widely advertised claim that its methods of genetically modifying food crops are "specific, precise, and predictable" and therefore safe. In short, the most dramatic achievement to date of the \$3 billion Human Genome Project is the refutation of its own scientific rationale.

Since Crick first proposed it forty-four years ago, the central dogma has come to dominate biomedical research. Simple, elegant and easily summarized, it seeks to reduce inheritance, a property that only living things possess, to molecular dimensions: the molecular agent of inheritance is DNA, deoxyribonucleic acid, a very long, linear molecule tightly coiled within each cell's nucleus. DNA is made up of four different kinds of nucleotides, strung together in each gene in a particular linear order of sequence. Segments of DNA comprise the genes that, through a series of molecular processes, give rise to each of our inherited traits.

Guided by Crick's theory, the Human Genome Project was intended to identify and enumerate all of the genes in the human body by working out the sequence of the three billion nucleotides in human DNA. In 1990, James Watson described the Human Genome Project as "the ultimate description of life." It will yield, he claimed, the information "that determines if you have life as a fly, a carrot, or a man." Walter Gilbert, one of the project's earliest proponents, famously observed that the 3 billion nucleotides found in human DNA would easily fit on a compact disc, to which one could point and say, "here is a human being; it's me!" President Bill Clinton described the human genome as "the language in which God created life." How could the minute dissection of human DNA into a sequence of 3 billion nucleotides support such hyperbolic claims? Crick's crisply stated theory attempts to answer that question. It hypothesizes a clear-cut chain of molecular processes that leads from a single DNA gene to the appearance of a particular inherited trait. The explanatory power of the theory is based on an extravagant proposition: that the DNA genes have unique, absolute, and universal control over the totality of inheritance in all forms of life.

In order to control inheritance, Crick reasoned, genes would need to govern the synthesis of protein, since proteins form the cell's internal structures and, as enzymes, catalyze the chemical events that produce specific inherited traits. The ability of DNA to govern the synthesis of protein is facilitated by their similar structures -- both are linear molecules composed of specific sequences of subunits. A particular gene is distinguished from another by the precise linear order (sequence) in which the four different nucleotides appear in its DNA. In the same way, a particular protein is distinguished from another by the specific sequence of the twenty different kinds of amino acids of which it is made. The four kinds of nucleotides can be arranged in numerous possible sequences, and the choice of any one of them in the makeup of a particular gene represents its "genetic information" in the same sense that, in poker, the order of a hand of cards informs the player whether to bet high on a

straight or drop out with a meaningless set of random numbers.

Crick's "sequence hypothesis" neatly links the gene to the protein: the sequence of the nucleotides in a gene "is a simple code for the amino acid sequence of a particular protein." This is shorthand for a series of well-documented molecular processes that transcribe the gene's DNA nucleotide sequence into a complementary sequence of ribonucleic acid (RNA) nucleotides that, in turn, delivers the gene's code to the site of protein formation, where it determines the sequential order in which the different amino acids are linked to form the protein. It follows that in each living thing there should be a one-to-one correspondence between the total number of genes and the total number of proteins. The entire array of human genes -- that is, the genome -- must therefore represent the whole of a person's inheritance, which distinguishes a person from a fly, or Walter Gilbert from anyone else. Finally, because DNA is made of the same four nucleotides in every living thing, the genetic code is universal, which means that a gene should be capable of producing its particular protein wherever it happens to find itself, even in a different species.

Crick's theory includes a second doctrine, which he originally called the "central dogma" (though this term is now generally used to identify his theory as a whole). The hypothesis is typical Crick: simple precise, and magisterial. "Once (sequential) information has passed into protein it cannot get out again." This means that genetic information originates in the DNA nucleotide sequence and terminates, unchanged, in the protein amino acid sequence. The pronouncement is crucial to the explanatory power of the theory because it endows the gene with undiluted control over the identity of the protein and the inherited trait that the protein creates. To stress the importance of their genetic taboo, Crick bet the future of the entire enterprise on it, asserting that "the discovery of just one type of present-day cell" in which genetic information passed from protein to nucleic acid or from protein to protein "would shake the whole intellectual basis of molecular biology."

Crick was aware of the brashness of his bet, for it was known that in living cells proteins come into promiscuous molecular contact with numerous other proteins and with molecules of DNA and RNA. His insistence that these interactions are genetically chaste was designed to protect the DNA's genetic message -- the gene's nucleotide sequence -- from molecular intruders that might change the sequence or add new ones as it was transferred, step by step, from gene to protein and thus destroy the theory's elegant simplicity.

Last February, Crick's gamble suffered a spectacular loss. In the journals *Nature* and *Science*, and at joint press conferences and television appearances, the two genome research teams reported their results. The major result was "unexpected." Instead of the 100,000 or more genes predicted by the estimated number of human proteins, the gene count was only about 30,000. By this measure, people are only about as gene-rich as a mustardlike weed (which has 26,000 genes) and about twice as genetically endowed as a fruit fly or a primitive worm -- hardly an adequate basis for distinguishing among "life as a fly, a carrot, or a man." In fact, an inattentive reader of genomic CDs might easily mistake Walter Gilbert for a mouse, 99 percent of whose genes have human counterparts.

The surprising results contradicted the scientific premise on which the genome project was undertaken and dethroned its guiding theory, the central dogma. After all, if the human gene count is too low to match the number of proteins and the numerous inherited traits that they

engender, and if it cannot explain the vast inherited difference between a weed and a person, there must be much more to the "ultimate description of life" than the genes, on their own, can tell us.

Scientists and journalists somehow failed to notice what had happened. The discovery that the human genome is not much different from the roundworm's, led Dr. Eric Lander, one of the leaders of the project, to declare that humanity should learn "a lesson in humility." In the *New York Times*, Nicholas Wade merely observed that the project's surprising results will have an "impact on human pride" and that "human self-esteem may be in for further blows" from future genome analyses, which had already found that the genes of mice and men are very similar.

The project's scientific reports offered little to explain the shortfall in the gene count. One of the possible explanations for why the gene count is "so discordant with our predictions" was described, in full, last February in *Science* as follows: "nearly 40% of human genes are alternatively spliced." Properly understood, this modest, if esoteric, account fulfills Crick's dire prophecy: it "shakes the whole intellectual basis of molecular biology" and undermines the scientific validity of its applications to genetic engineering.

Alternative splicing is a startling departure from the orderly design of the central dogma, in which the distinctive nucleotide sequence of a single gene encodes the amino acid sequence of a single protein. According to Crick's sequence hypothesis, the gene's nucleotide sequence (i.e., its "genetic information") is transmitted, altered in form but not in content, through RNA intermediaries, to the distinctive amino acid sequence of a particular protein. In alternative splicing, however, the gene's original nucleotide sequence is split into fragments that are then recombined in different ways to encode a multiplicity of proteins, each of them different in their amino acid sequence from each other and from the sequence that the original gene, if left intact, would encode.

The molecular events that accomplish this genetic reshuffling are focused on a particular stage in the overall DNA-RNA-protein, progression. It occurs when the DNA gene's nucleotide sequence is transferred to the next genetic carrier -- messenger RNA. A specialized group of fifty to sixty proteins, together with five small molecules of RNA -- known as a "spliceosome" -- assembles at sites along the length of the messenger RNA, where it cuts apart various segments of the messenger RNA. Certain of these fragments are spliced together into a number of alternative combinations, which then have nucleotide sequences that differ from the gene's original one. These numerous, redesigned messenger RNAs govern the production of an equal number of proteins that differ in their amino acid sequence and hence in the inherited traits that they engender. For example, when the word TIME is rearranged to read MITE, EMIT, and ITEM, three alternative units of information are created from an original one. Although the original word (the unspliced messenger RNA nucleotide sequence) is essential to the process, so is the agent that performs the rearrangement (the spliceosome).

Alternative splicing can have an extraordinary impact on the gene/protein ratio. We now know that a single gene originally believed to encode a single protein that occurs in cells of the inner ear of chicks (and of humans) gives rise to 576 variant proteins, differing in their amino acid sequences. The current record for the number of different proteins produced from

a single gene by alternative splicing is held by the fruit fly, in which one gene generates up to 38,016 variant protein molecules.

Alternative splicing thus has a devastating impact on Crick's theory: it breaks open the hypothesized isolation of the molecular system that transfers genetic information from a single gene to a single protein. By rearranging the single gene's nucleotide sequence into a multiplicity of new messenger RNA sequences, each of them different from the unspliced original, alternative splicing can be said to generate *new* genetic information. Certain of the spliceosome's proteins and RNA components have an affinity for particular sites and, binding to them, form an active catalyst that cuts the messenger RNA and then rejoins the resulting fragments. The spliceosome proteins thus contribute to the added genetic information that alternative splicing creates. But this conclusion conflicts with Crick's second hypothesis -- that proteins cannot transmit genetic information to nucleic acid (in this case, messenger RNA) -- and shatters the elegant logic of Crick's interlocking duo of genetic hypotheses.

The discovery of alternative splicing also bluntly contradicts the precept that motivated the genome project. It nullifies the exclusiveness of the gene's hold on the molecular process of inheritance and disproves the notion that by counting genes one can specify the array of proteins that define the scope of human inheritance. The gene's effect on inheritance thus cannot be predicted simply from its nucleotide sequence -- determination of which is one of the main purposes of the Human Genome Project. Perhaps this is why the crucial role of alternative splicing seems to have been ignored in the planning of the project and has been obscured by the cunning manner in which its chief result has been reported. Although the genome reports do not mention it, alternative splicing was discovered well before the genome project was even planned -- in 1978 in virus replication, and in 1981 in human cells. By 1989, when the Human Genome Project was still being debated among molecular biologists, its champions were surely aware that more than 200 scientific papers on alternative splicing of human genes had already been published. Thus, the shortfall in the human gene count could -- indeed should -- have been predicted. It is difficult to avoid the conclusion -- troublesome as it is -- that the project's planners knew in advance that the mismatch between the numbers of genes and proteins in the human genome was to be expected, and that the \$3 billion project could not be justified by the extravagant claims that the genome -- or perhaps God speaking through it -- would tell us who we are.

Alternative splicing is not the only discovery over the last forty years that has contradicted basic precepts of the central dogma. Other research has tended to erode the centrality of the DNA double helix itself, the theory's ubiquitous icon. In their original description of the discovery of DNA, Watson and Crick commented that the helix's structure "immediately suggests a possible copying mechanism for the genetic material." Such self-duplication is the crucial feature of life, and in ascribing it to DNA, Watson and Crick concluded, a bit prematurely, that they had discovered life's magic molecular key.

Biological replication does include the precise duplication of DNA, but this is accomplished by the living cell, not by the DNA molecule alone. In the development of a person from a single fertilized egg, the egg cell and the multitude of succeeding cells divide in two. Each such division is preceded by a doubling of the cell's DNA; two new DNA strands are produced by attaching the necessary nucleotides (freely available in the cell), in the proper

order, to each of the two DNA strands entwined in the double helix. As the single fertilized egg cell grows into an adult, the genome is replicated many billions of times, its precise sequence of three billion nucleotides retained with extraordinary fidelity. The rate of error -- that is, the insertion into the newly made DNA sequence of a nucleotide out of its proper order -- is about one in 10 billion nucleotides. But on its own, DNA is incapable of such faithful replication; in a test-tube experiment, a DNA strand, provided with a mixture of its four constituent nucleotides, will line them up with about one in a hundred of them out its proper place. On the other hand, when the appropriate protein enzymes are added to the test tube, the fidelity with which nucleotides are incorporated in the newly made DNA strand is greatly improved, reducing the error rate to one in 10 million. These remaining errors are finally reduced to one in 10 billion by a set of "repair" enzymes (also proteins) that detect and remove mismatched nucleotides from the newly synthesized DNA.

Thus, in the living cell the gene's nucleotide code can be replicated faithfully only because an array of specialized proteins intervenes to prevent most of the errors -- which DNA by itself is prone to make -- and to repair the few remaining ones. Moreover, it has been known since the 1960s that the enzymes that synthesize DNA influence its nucleotide sequence. In this sense, genetic information arises not from DNA alone but through its essential collaboration with protein enzymes -- a contradiction of the central dogma's precept that inheritance is uniquely governed by the self-replication of the DNA double helix.

Another important divergent observation is the following: in order to become biochemically active and actually generate the inherited trait, the newly made protein, a strung-out ribbon of a molecule, must be folded up into a precisely organized ball-like structure. The biochemical events that give rise to genetic traits -- for example, enzyme action that synthesizes a particular eye-color pigment -- take place at specific locations on the outer surface of the three-dimensional protein, which is created by the particular way in which the molecule is folded into that structure. To preserve the simplicity of the central dogma, Crick was required to assume, without any supporting evidence, that the nascent protein -- a linear molecule -- always folded itself up in the right way once its amino acid sequence had been determined. In the 1980s, however, it was discovered that some nascent proteins are on their own likely to become misfolded -- and therefore remain biochemically inactive -- unless they come in contact with a special type of "chaperone" protein that properly folds them.

The importance of these chaperones has been underlined in recent years by research on degenerative brain diseases that are caused by "prions," research that has produced some of the most disturbing evidence that the central dogma is dangerously misconceived. Crick's theory holds that biological replication, which is essential to an organism's ability to infect another organism, cannot occur without nucleic acid. Yet when scrapie, the earliest known such disease, was analyzed biochemically, no nucleic acid -- neither DNA nor RNA -- could be found in the infectious material that transmitted the disease. In the 1980's, Stanley Prusiner confirmed that the infectious agents that cause scrapie, mad cow disease, and similar very rare but invariably fatal human diseases are indeed nucleic-acid-free proteins (he named them prions), which replicate in an entirely unprecedented way. Invading the brain, the prion encounters a normal brain protein which it then refolds to match the prion's distinctive three-dimensional shape. The newly refolded protein itself becomes infectious and, acting on another molecule of the normal protein, sets up a chain reaction that propagates the disease to its fatal end.

The prion's unusual behavior raises important questions about the connection between a protein's amino acid sequence and its biochemically active, folded-up structure. Crick assumed that the proteins' active structure is automatically determined by its amino acid sequence (which is, after all, the sign of its genetic specificity), so that two proteins with the same sequence ought to be identical in their activity. The prion violates this rule. In a scrapie-infected sheep, the prion and the brain protein that it refolds have the same amino acid sequence, but one is a normal cellular component and the other is a fatal infectious agent. This suggests that the protein's folded-up configuration is, to some degree, independent of its amino acid sequence and therefore determined, in part, by something other than the DNA gene that governed the synthesis of that sequence. And since the prion protein's three-dimensional shape is endowed with transmissible genetic information, it violates another fundamental Crick precept as well -- the forbidden passage of genetic information from one protein to another. Thus, what is known about the prion is a somber warning that processes far removed from the conceptual constraints of the central dogma are at work in molecular genetics and can lead to fatal disease.

By the mid 1980s, therefore, long before the \$3 billion Human Genome Project was funded, and long before genetically modified crops began to appear in our fields, a series of protein-based processes had already intruded on the DNA gene's exclusive genetic franchise. An array of protein enzymes must repair the all-too-frequent mistakes in gene replication and in the transmission of the genetic code to proteins as well. Certain proteins, assembled in spliceosomes, can reshuffle the RNA transcripts, creating hundreds and even thousands of different proteins from a single gene. A family of chaperones, proteins that facilitate the proper folding -- and therefore the biochemical activity -- of newly made proteins, form an essential part of the gene-to-protein process. By any reasonable measure, these results contradict the central dogma's cardinal maxim: that a DNA gene exclusively governs the molecular processes that give rise to a particular inherited trait. The DNA gene clearly exerts an important influence on inheritance, but it is not unique in that respect and acts only in collaboration with a multitude of protein-based processes that prevent and repair incorrect sequences, transform the nascent protein into its folded, active form, and provide crucial added genetic information well beyond that originating in the gene itself. The net outcome is that no single DNA gene is the sole source of a given protein's genetic information and therefore of the inherited trait.

The credibility of the Human Genome Project is not the only casualty of the scientific community's stubborn resistance to experimental results that contradict the central dogma. Nor is it the most significant casualty. The fact that one gene can give rise to multiple proteins also destroys the theoretical foundation of a multibillion-dollar industry, the genetic engineering of food crops. In genetic engineering it is assumed, without adequate experimental proof, that a bacterial gene for an insecticidal protein, for example, transferred to a corn plant, will produce precisely that protein and nothing else. Yet in that alien genetic environment, alternative splicing of the bacterial gene might give rise to multiple variants of the intended protein -- or even to proteins bearing little structural relationship to the original one, with unpredictable effects on ecosystems and human health.

The delay in dethroning the all-powerful gene led in the 1990s to a massive invasion of genetic engineering into American agriculture, though its scientific justification had already been compromised a decade or more earlier. Nevertheless, ignoring the profound fact that in

nature the normal exchange of genetic material occurs exclusively within a single species, biotech-industry executives have repeatedly boasted that, in comparison, moving a gene from one species to another is not only normal but also more specific, precise, and predictable. In only the last five years such transgenic crops have taken over 68 percent of the US soybean acreage, 26 percent of the corn acreage, and more than 69 percent of the cotton acreage.

That the industry is guided by the central dogma was made explicit by Ralph W.F. Hardy, president of the National Agricultural Biotechnology Council and formerly director of life sciences at DuPont, a major producer of genetically engineered seeds. In 1999, in Senate testimony, he succinctly described the industry's guiding theory this way: "DNA (top management molecules) directs RNA formation (middle management molecules) directs protein formation (worker molecules)." The outcome of transferring a bacterial gene into a corn plant is expected to be as predictable as the result of a corporate takeover: what the workers do will be determined precisely by what the new top management tells them to do. This Reaganesque version of the central dogma is the scientific foundation upon which each year billions of transgenic plants of soybeans, corn, and cotton are grown with the expectation that the particular alien gene in each of them will be faithfully replicated in each of the billions of cell divisions that occur as each plant develops; that in each of the resultant cells the alien gene will encode only a protein with precisely the amino acid sequence that it encodes in its original organism; and that throughout this biological saga, despite the alien presence, the plant's natural complement of DNA will itself be properly replicated with no abnormal changes in composition.

In an ordinary unmodified plant the reliability of this natural genetic process results from the compatibility between its gene system and its equally necessary protein-mediated systems. The harmonious relation between the two systems develops during their cohabitation, in the same species, over very long evolutionary periods, in which natural selection eliminates incompatible variants. In other words, within a single species the reliability of the successful outcome of the complex molecular process that gives rise to the inheritance of particular traits is guaranteed by many thousands of years of testing, in nature.

In a genetically engineered transgenic plant, however, the alien transplanted bacterial gene must properly interact with the plants' protein-mediated systems. Higher plants, such as corn, soybeans, and cotton, are known to possess proteins that repair DNA miscoding; proteins that alternatively splice messenger RNA and thereby produce a multiplicity of different proteins from a single gene; and proteins that chaperone the proper folding of other, nascent proteins. But the plant systems' evolutionary history is very different from the bacterial gene's. As a result, in the transgenic plant the harmonious interdependence of the alien gene and the new host's protein-mediated systems is likely to be disrupted in unspecified imprecise and inherently unpredictable ways. In practice, these disruptions are revealed by the numerous experimental failures that occur before a transgenic organism is actually produced and by unexpected genetic changes that occur even when the gene has been successfully transferred.

Most alarming is the recent evidence that in a widely grown genetically modified food crop -- soybeans containing an alien gene for herbicide resistance -- the transgenic host plant's genome has itself been unwittingly altered. The Monsanto Company admitted in 2000 that

its soybeans contained some extra fragments of the transferred gene, but nevertheless concluded that "no new proteins were expected or observed to be produced." A year later, Belgian researchers discovered that a segment of the plant's own DNA had been scrambled. The abnormal DNA was large enough to produce a new protein, a potentially harmful protein.

One way that such mystery DNA might arise is suggested by a recent study showing that in some plants carrying a bacterial gene, the plant's enzymes that correct DNA replication errors rearrange the alien gene's nucleotide sequence. The consequences of such changes cannot be foreseen. The likelihood in genetically engineered crops of even exceedingly rare, disruptive effects of gene transfer is greatly amplified by the billions of individual transgenic plants already being grown annually in the United States.

The degree to which such disruptions do occur in genetically modified crops is not known at present, because the biotechnology industry is not required to provide even the most basic information about the actual composition of the transgenic plants to the regulatory agencies. No tests, for example, are required to show that the plant actually produces a protein with the same amino acid sequence as the original bacterial protein. Yet, this information is the only way to confirm that the transferred gene does in fact yield the theory-predicted product. Moreover, there are no required studies based on detailed analysis of the molecular structure and biochemical activity of the alien gene and its protein product in the transgenic commercial crop. Given that some unexpected effects may develop very slowly, crop plants should be monitored in successive generations as well. None of these essential tests are being performed, and billions of transgenic plants are now being grown with only the most rudimentary knowledge about the resulting changes in their composition. Without detailed, ongoing analyses of the transgenic crops, there is no way of knowing if hazardous consequences might arise. Given the failure of the central dogma, there is no assurance that they will not. The genetically engineered crops now being grown represent a massive uncontrolled experiment whose outcome is inherently unpredictable. The results could be catastrophic.

Crick's central dogma has played a powerful role in creating both the Human Genome Project and the unregulated spread of genetically engineered food crops. Yet as evidence that contradicts this governing theory has accumulated, it has had no effect on the decisions that brought both of these monumental undertakings into being. It is true that most of the experimental results generated by the theory confirmed the concept that genetic information, in the form of DNA nucleotide sequences, is transmitted from DNA via RNA to protein. But other observations have contradicted the one-to-one correspondence of gene to protein and have broken the DNA gene's exclusive franchise on the molecular explanation of heredity. In the ordinary course of science, such new facts would be woven into the theory, adding to its complexity, redefining its meaning, or, as necessary, challenging its basic premise. Scientific theories are meant to be falsifiable; this is precisely what makes them scientific theories. The central dogma has been immune to this process. Divergent evidence is duly reported and, often enough generates intense research, but its clash with the governing theory is almost never noted.

Because of their commitment to an obsolete theory, most molecular biologists operate under the assumption that DNA is the secret of life, whereas the careful observation of the

hierarchy of living processes strongly suggests that it is the other way around: DNA did not create life; life created DNA. When life was first formed on the earth, proteins must have appeared before DNA because, unlike DNA, proteins have the catalytic ability to generate the chemical energy needed to assemble small ambient molecules into larger ones such as DNA. DNA is a mechanism created by the cell. Early life survived because it grew, building up its characteristic array of complex molecules. It must have been a sloppy kind of growth; what was newly made did not exactly replicate what was already there. But once produced by the primitive cell, DNA could become a stable place to store structural information about the cell's chaotic chemistry, something like the minutes taken by a secretary at a noisy committee meeting. There can be no doubt that the emergence of DNA was a crucial stage in the development of life, but we must avoid the mistake of reducing life to a master molecule in order to satisfy our emotional need for unambiguous simplicity. The experimental data, shorn of dogmatic theories, points to the irreducibility of the living cell, the inherent complexity of which suggests that any artificially altered genetic system, given the magnitude of our ignorance, must sooner or later give rise to unintended, potentially disastrous, consequences. We must be willing to recognize how little we truly understand about the secrets of the cell, the fundamental unit of life.

Why, then, has the central dogma continued to stand? To some degree the theory has been protected from criticism by a device more common to religion than science; dissent, or merely the discovery of a discordant fact, is a punishable offense, a heresy that might easily lead to professional ostracism. Much of this bias can be attributed to institutional inertia, a failure of rigor, but there are other, more insidious, reasons why molecular geneticists might be satisfied with the status quo; the central dogma has given them such a satisfying, seductively simplistic explanation of heredity that it seemed sacrilegious to entertain doubts. The central dogma was simply too good not to be true.

As a result, funding for molecular genetics has rapidly increased over the last twenty years, new academic institutions, many of them "genomic" variants of more mundane professions, such as public health, have proliferated. At Harvard and other universities, the biology curriculum has become centered on the genome. But beyond the traditional scientific economy of prestige and the generous funding that follows it as night follows day, money has distorted the scientific process as a once purely academic pursuit has been commercialized to an astonishing degree by the researchers themselves. Biology has become a glittering target for venture capital; each new discovery brings new patents, new partnerships, and new corporate affiliations. But as the growing opposition to transgenic crops clearly shows, there is persistent public concern not only with the safety of genetically engineered foods but also with the inherent dangers in arbitrarily overriding patterns of inheritance that are embedded in the natural world through long evolutionary experience. Too often those concerns have been derided by industry scientists as the "irrational" fears of an uneducated public. The irony, of course, is that the biotechnology industry is based on science that is forty years old and conveniently devoid of more recent results, which show that there are strong reasons to fear the potential consequences of transferring a DNA gene between species. What the public fears is not the experimental science but the fundamentally irrational decision to let it out of the laboratory into the real world before we truly understand it.

Barry Commoner is senior scientist at the Center for Biology of Natural Systems at Queen's College, City University of New York where he directs the Critical Genetics Project. Readers can obtain a list of references used as sources for this article by sending a request to: cbns@cbns.qc.edu

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