Syracuse Scholar (1979-1991)

Volume 7
Issue 1 *Syracuse Scholar Spring 1986*

Article 3

4-15-1986

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NINA V. FEDOROFF

RECOMBINANT DNA EXPERIMENTATION has been with us for more than a decade, embattled since its inception. Scientists have been questioned and have questioned themselves about the safety and advisability of their experiments. The public has been bombarded on the one hand by scare headlines suggesting that scientists are making dangerous organisms or might well make them by accident and on the other by hype promising such genetic engineering wonders as plants that pump gas directly into one's automobile. Not surprisingly, there are neither monsters nor miracles in the reality of genetic engineering. Yet the real story, the real history of this particular scientific development, is both fascinating and deeply puzzling. It is indeed the story of a substantial scientific breakthrough, one whose impact on basic biological knowledge has already been profound and whose future can only be glimpsed. But it is much more than that. It is the story of the first concerted effort by scientists to foresee and forestall the possibility of harm, however inadvertent. It is the history of that extraordinarily well-intentioned effort somehow gone sour, the public unsure what to believe and scientists sure only that the controversy became unbelievable. It is a contemporary cautionary tale of science and public policy, of scientists and bureaucrats and crusaders. It is about the process of defining a new kind of dialogue between science and society and the attendant difficulties and near derailments.

This essay evolved out of a lecture I gave as a Phi Beta Kappa Visiting Scholar during the 1984–85 academic year, when recombinant DNA, after several years' adumbration, again hit the headlines. In reworking it for publication, I have tried to preserve its several original objectives. The first of these was to communicate some sense of what recombinant DNA technology is about scientifically, where it comes from historically and where it might realistically lead us in the future. My second objective was to recount briefly the history of the

recombinant DNA controversy, beginning with the concerns expressed by scientists more than a decade ago about the potential hazards of recombining DNA molecules and ending with the current debate over gene transfer and release into the environment of genetically engineered organisms. My third objective was to gain some perspective on the situation and to include students in my own continuing struggles to distinguish the real from the specious issues and critics and to make public policy wisely in acknowledged ignorance. I have omitted my original detailed description of recombinant DNA techniques, not because I thought it unimportant, but because of John Vournakis's excellent essay on the subject in a previous issue of the *Scholar.*[1]

1. John N. Vournakis, "Genetic Engineering and Recombinant DNA," *Syracuse Scholar* 5 (Fall 1984): 57–65.

IT IS A POPULAR MISCONCEPTION that recombinant DNA technology is about cloning organisms: plants, animals, and even people. It isn't. It is about cloning genes, bits of DNA. Perhaps an analogy will make the difference more meaningful. An automobile is a rather complex machine assembled from many simple parts, some as simple as a screw. For each part, even each screw, there exists a plan, a set of specifications. If one were to obtain and make a million copies of the specifications on a copying machine, one would have done something quite analogous to what the recombinant DNA technician or gene cloner does. The million sheets of paper cannot be confused with a million cars. The many copies of a gene generated through recombinant DNA technology stand in precisely the same relation to the organism from which the gene was isolated as does the stack of paper to the car. Indeed the analogy is quite apt because a gene is basically a set of instructions. Genes contain in coded form the instructions for assembling another molecule, usually a protein. Proteins are big molecules; we call them macromolecules. Proteins make up much of the structure and substance of all living organisms. They also do the work that goes on in an organism: extracting energy from food and converting it to usable form, moving, and growing. Genes are blueprints; they are the instructions for making a tree or a butterfly. Genes are what heredity is all about; they are its elementary units. Genes are what we pass to our offspring to make them irritatingly and endearingly like us.

We know that heredity has fascinated human beings throughout recorded history and the fascination undoubtedly began before that. Humans had an intuitive grasp of heredity and genetics long before they knew what genes were, and they used that knowledge to carry out what we now give the rather sinister designation "genetic manipulation." Traditional genetic manipulation is called breeding. Humans have bred and continue to breed plants and animals for a variety of purposes, ranging from increased food value at the practical end of the spectrum to aesthetic pleasure at the artistic end. Breeding is the mating or genetic crossing of individuals with desirable characteristics to obtain new or better combinations of traits in the offspring. Breeding isn't a very efficient process, since it involves discarding most of the progeny, selecting just a few for further propagation. But selective

breeding can be (and was) done with no knowledge of genes or genetics, and it is an extremely effective method of genetic manipulation. Indeed, one of the arguments that Charles Darwin used to support his hypothesis of natural selection as a major force in the long-term biological change that he called evolution was the extraordinary effectiveness of the artificial selection techniques used by human beings in the breeding of plants and animals.

The point of all this is that the practice of genetic manipulation, of creating and propagating new combinations of genes, is a very old one in human culture. What is new is that we have learned enough to do it less haphazardly than traditional methods allow. We are now able to isolate and move a single gene at a time. We can also move genes between very different organisms, with the potential of eliminating barriers that have long frustrated the breeder. Our present genetic capabilities are very much a product of this century, but the extraordinary growth in our genetic knowledge began almost half a century earlier with the experiments of the monk Gregor Mendel on peas. The results of his experiments were published in 1865 but received essentially no attention until the turn of the century, when his work was discovered and appreciated by several European botanists. In describing Mendel's experiments in 1902, the biologist William Bateson wrote, "An exact determination of the laws of heredity will probably work more change in man's outlook on the world, and in his power over nature, than any other advance in natural knowledge that can be foreseen."[2]

2. William Bateson, "Problems of Heredity as a Subject for Horticultural Investigation," *William Bateson, F.R.S. Naturalist,* ed. Beatrice Bateson (London: Cambridge University Press, 1928), p. 171.

Although one must acknowledge a few influential advances that were not foreseen, Bateson's statement remains remarkably prescient. Mendel's work, or perhaps the rediscovery of his work, clearly marks the beginning of this century's explosion of genetic knowledge. The first decades of the century saw the confirmation, consolidation, and generalization of what came to be called Mendel's laws, rules that describe the hereditary behavior of genes. Genes were defined as the units of heredity and, as more and more genes were identified, it became evident that they could be arranged in sets of linear arrays that acted as units. In time, we learned that the linear arrays corresponded to structures in the nucleus: the chromosomes, the physical bearers of genes. During the 1940s and 1950s, the chemical nature of the genetic material was identified as deoxyribonucleic acid (DNA), and the DNA molecule was understood to be a long, helical polymer comprising two complementary strands, the familiar double helix. The structure of DNA, worked on by many but worked out by James Watson and Francis Crick, had substantial explanatory power for heredity. Inherent in the chemical structure was the explanation for hereditary constancy. Each strand of the double helix acts as a template for the assembly of a complementary strand, resulting in the creation of two daughter DNA helices having the same structure and information as the parent DNA molecule.

Genetics and biochemistry came together in an enormously productive way during the 1950s and 1960s to provide an understanding of how information is stored in the DNA molecule and how DNA is

replicated. We learned how information is encoded in the linear sequence of the four different structural subunits in DNA, the nucleotides. We learned, too, how the cell decoded the information to convert it to protein structure and to the structure of ribonucleic acid, the cell's other informational nucleic acid. We understood how the hereditary material, the DNA, is replicated. We learned that there are proteins, called enzymes, which made the nucleotide subunits. There are enzymes that polymerize or link together the nucleotides on the appropriate DNA template and others that repair the mistakes the first ones make. All in all, we came to appreciate the exquisite fidelity with which the hereditary molecule is replicated, a fidelity inherent in Mendel's laws. But we also learned that change or mutation is inherent in the chemistry of the nucleotides and the replication mechanism, providing a molecular explanation for the origin of the differences between organisms that Darwin believed to be central to biological evolution.

AS OUR KNOWLEDGE OF HOW DNA IS USED, replicated, and otherwise processed in the cells grew, so did our ability to manipulate DNA in the laboratory. One fact that emerged during this period that proved seminal for the development of our present recombinant DNA technology was that certain bacteria have the ability to tell the difference between their own hereditary material and DNA from other organisms. What they have are certain enzymes, called restriction endonucleases, that can cut the DNA very precisely at special sequences in such a way that the cut ends are, in effect, "sticky." The stickiness results because the restriction enzymes cut the two strands of the DNA molecule at slightly different places, leaving protruding single-stranded ends. The overhanging single-stranded ends of two molecules are held together by the chemical forces that keep the complementary strands of the DNA double helix together. The reason that these enzymes allow the bacterial cell to distinguish its own DNA from foreign DNA is that the bacterial cell has another enzyme that covers, but only in its own DNA, the target sequence that the enzyme cuts. The bacterial enzyme can therefore destroy invading DNA, but not its own. This odd little bacterial defense tactic provided one of the essential elements for the development of contemporary recombinant DNA technology, because DNAs from very different sources can be cut with the same restriction enzyme and put together or "recombined" via their sticky ends. The recombined or recombinant DNA molecules can then be ligated or sealed together permanently by another DNA-processing enzyme, appropriately called a ligase.[3]

Another important discovery that contributed to the development of recombinant DNA technology was that the bacterial chromosome isn't the only DNA molecule in a bacterial cell. Bacteria have, in addition to their chromosome, tiny circular DNA molecules called plasmids. Plasmids generally outreplicate the bacterial chromosome. Moreover, they can sustain genetic changes or mutations that allow

3. See Vournakis, "Genetic Engineering," for a more detailed account of the molecular technology.

them to exist in very large numbers in the bacterial cell. The ability of plasmids to replicate themselves many times over provides the means of cloning recombinant DNA molecules. If a plasmid is cut with a restriction enzyme, recombined and ligated with DNA from another source (be it elephant or butterfly), and returned to the bacterium, the bacterium and its progeny will copy and recopy the recombinant DNA molecule millions of times, much like the copying machine I used in my analogy. The copying is the cloning, for it produces millions of identical copies of the DNA that was originally inserted into the plasmid. This is important to the molecular biologist because one simply cannot see or study a single molecule of anything. Imagine studying the properties of water (or even quenching your thirst) if you had only one molecule of it. A glassful of water contains a million times a billion times a billion molecules of water. Recombinant DNA technology lets the molecular biologist turn a single recombinant DNA molecule into a teaspoonful of DNA. And with even a teaspoonful of a pure gene, the resourceful molecular biologist can begin to quench his or her thirst to know how a gene is put together and how it works.

Why, then, is recombinant DNA technology so terrific or terrifying, depending on your perspective? First, it is important to appreciate that processes very similar to those I have just described occur naturally. There are plasmids that can insert themselves into the bacterial chromosome and come out again, having picked up a bacterial gene or two. There are also transposable genes, genes that can jump from one chromosome to another. And most plasmids (although not those used for cloning) have a naturally evolved system for traveling from bacterium to bacterium. Thus there are natural mechanisms for cloning genes, many of which were exploited by bacterial geneticists long before the development of recombinant DNA techniques. The reason that recombinant DNA techniques are so important is simply that they make it possible for us to reach a completely new level in our understanding of how complex organisms function. Before the development of these techniques, we had achieved a reasonably good understanding of the basic biochemical principles at work in all organisms. This had been accomplished largely through the use of very simple model organisms or bacterial systems in which one could use natural gene cloning mechanisms to isolate a gene of interest. But the genes of complex higher organisms, the very organisms we wanted most to know about, were not accessible to study by available techniques. We were rather in the position of a student on the steps of a locked library. He might know quite well what books are made of, the language in which they are written and how they are filed on the shelves, but unless he can get into the library, withdraw a book or two, and begin to read, he will never understand the information content of the library. And that is just where we were in our study of genes in higher organisms. We knew what genes were made of, how information was generally stored in them, and even a good deal about where they were located on the chromosomes. But recombinant DNA techniques made it possible to isolate and study one gene at a time.

I WILL USE A COUPLE OF EXAMPLES to illustrate what these techniques have already allowed us to learn and what they will enable us to do in the foreseeable future.

Before these techniques were developed, we knew that higher organisms had genes that contained the information for making hemoglobin, the red blood cell protein that carries oxygen from the lungs to the cells in all the parts of the body. Hemoglobin genes have now been cloned both from normal individuals and from individuals with a variety of diseases affecting the hemoglobin. These include the familiar and deadly sickle-cell anemias and thalassemias. What has emerged is that the genes themselves are defective in these diseases. The amount of gene damage can be small or quite large: an abnormal gene can differ from a normal one by just a single nucleotide or it can have a large gap, termed a deletion, in it. Some patients are even missing entire hemoglobin genes. Scientists are currently developing methods that should make it possible to transplant cloned normal hemoglobin genes into patients with defective genes, just as we can now give blood transfusions, transplant internal organs, or treat people with insulin. There are other examples, perhaps a bit less dramatic, of the medical utility of recombinant DNA technology. These include the large-scale production of human insulin from cloned genes and of human growth hormone. Recombinant DNA technology has facilitated and made safer the development of vaccines for a number of human and animal diseases, including hepatitis virus and hoof-and-mouth disease. Recombinant DNA techniques have proved important in vaccine development because they allow the scientist to work with just part of the viral genes at a time. He or she no longer has to work with the entire, sometimes highly lethal or debilitating virus.

Another example of the power of recombinant DNA techniques comes from my own work on the transposable elements of corn plants. I have already mentioned the existence of jumping genes in bacteria. Their proper name is transposable elements and they are numerous and widespread in nature. They weren't even discovered in bacteria but in maize plants, about forty years ago, by Barbara McClintock. McClintock, a classical geneticist, identified transposable elements as genes that did rather odd things. Unlike most genes, they did not always have a fixed chromosomal location but could occasionally pick up and move to a new place. Until they were isolated in my laboratory three years ago with the aid of recombinant DNA techniques, McClintock's transposable elements were just a genetic abstraction. We now have cloned copies of several of the elements and have analyzed their structure in great detail. We can now go on to the next step of putting them to work.

What kind of work might transposable elements be able to do? Transposable elements not only move around themselves but also move other genes around. We have so far relied solely on breeding and selection to move genes around in plants. Although these procedures have been very successful, they are limited. To begin with, it takes a long time, perhaps ten years, to develop a new crop strain, for example, that has good growth and yield characteristics, as well as a new

gene for disease resistance. Moreover, conventional breeding techniques are restricted to plants that will crossbreed. All organisms, including plants, will breed only with very closely related organisms. A cabbage and a cactus, for example, can grow side by side without making a cabbage-cactus hybrid because they are sexually incompatible. Yet these plants have a great deal in common at a fundamental genetic level. To use my book analogy again, each of these plants is like a different book. The words in the book may well be in the same language and one might even find a few identical sentences in both books, yet the information contained in each is clearly different. Nonetheless, it might also be that a sentence from one book, judiciously introduced, might enrich the other. And so it is with crop plants. If we could keep all of the information painstakingly assembled by the plant breeder in our extraordinary hybrid corn, but introduce an extra gene that confers resistance to a debilitating viral disease, it would be of enormous value. With the isolation of transposable elements, we have the means of moving such genes around. What we do not yet have, but should have soon, are genes that confer disease resistance. Thus recombinant DNA techniques should eventually allow us to enhance the plant breeder's work by the specific introduction of desirable single genes from a variety of sources.

IF I HAVE CONVEYED THE NOTION that the history of recombinant DNA experimentation is an untroubled scientific success story, I have not misrepresented the situation substantially. And yet we have been hearing about the *potential hazards* of recombinant DNA research for a decade. No reasonably well-informed individual in our society has escaped reading or hearing at least one account of the monsters that biotechnology might well bring, deliberately or by accident. What are the real dangers? Are serious scientists concerned or is this the stuff of science fiction?

These are questions not easily answered. Indeed, concern over potential hazards of certain recombinant DNA experiments began among scientists—not a fringe group with little knowledge of the subject but the very scientists centrally involved in the early stages of developing the techniques. This concern crystallized in an open letter to the scientific community, "Potential Biohazards of Recombinant DNA Molecules," published in *Science* in 1974. The letter was signed by eleven eminent molecular biologists, among them several Nobel laureates including James Watson, codiscoverer of the structure of DNA. The crux of the letter is contained in three sentences: "Several groups of scientists are now planning to use this technology to create recombinant DNA's from a variety of... viral, animal, and bacterial sources. Although such experiments are likely to facilitate the solution of important theoretical and practical biological problems, they would also result in the creation of novel types of infectious DNA elements whose biological properties cannot be completely predicted in advance. There is serious concern that some of these artificial recombinant DNA molecules could prove biologically hazardous."[4]

4. Paul Berg et al., *Science* 185 (1974): 303.

The authors of the letter went on to make some specific recommendations. First, they suggested that certain kinds of experiments, which they felt at the time to have the greatest chance of being hazardous, not be done for the moment. Second, they recommended that scientists themselves organize a meeting to discuss the potential hazards of the experiments. And third, they requested that the director of the National Institutes of Health (NIH) establish an advisory committee to oversee "an experimental program to evaluate the potential biological and ecological hazards of (certain kinds) of recombinant DNA molecules," develop procedures to minimize the spread of such molecules, and devise guidelines for investigators working with "potentially hazardous recombinant DNA molecules."

The suggestions of the letter-writing Berg Committee, as it came to be called after its chairman Paul Berg, were all implemented. An international conference was convened, the famous, contentious Asilomar conference, out of which emerged the first guidelines for experiments involving recombinant DNA and a call for a moratorium on certain kinds of experiments. The NIH also responded and established the Recombinant DNA Advisory Committee to elaborate the guidelines and to formulate studies assessing risk. The difficulty of the undertaking soon became apparent. Since the risks of recombinant DNA research were hypothetical, the guidelines could be based only on people's guesses about dangers. Scientists spent a considerable amount of time thinking up scenarios. With known hazards, such as radiation, this is a sensible procedure; one can calculate from the known effects of radiation on human beings the consequences of a radiation spill of a certain magnitude. But this cannot be done with hypothetical hazards for the simple reason that they are hypothetical. Lacking basic data, one tends to imagine the worst. So the guidelines for recombinant DNA research acquired an awesome aspect. They were written *as if* organisms with introduced genes were in fact quite dangerous. They specified that the work had to be done in special laboratories and had to employ debilitated organisms that had no chance of surviving in nature, even if someone were inadvertently to liberate the organisms in large quantities.

Although the necessity for new and stringent regulations was a matter of some contention among scientists from the beginning, what no one really foresaw was the intense, troubling, and debilitating public debate that arose over recombinant DNA. Since hindsight has a certain clarity that foresight lacks, one can see that what happened was, in some measure, predictable. If some of the best minds working on DNA say they are worried about the potential hazards of recombinant DNA, it is difficult to escape the suspicion that there really is something to worry about. What responsible public-policy maker would fail to heed the concerns the scientists themselves expressed? Who would not be in favor of the strictest regulations imaginable? Worse yet, if five years later the very same scientists said there was no hazard, who would not begin to wonder whether his or her faith in the knowledge and judgment of scientists was a bit misplaced?

Unfortunately, the fact that scientists of stature issued the first

words of caution lent support to the perception of imminent danger. The very existence and stringency of the guidelines came to imply that the experiments were unsafe. Amplified by a good deal of attention from the communications media, the recombinant DNA controversy reached everyone. The distinction between real, quantifiable hazards and potential hazards blurred and disappeared; people were quite apprehensive. Yet as the years passed, the accumulation of basic knowledge and experience with recombinant DNA, taken together with the results of risk-assessment studies, provided more and more evidence that recombinant DNA experiments were not inherently hazardous. Indeed, it is a bit ironic that some of the experiments originally thought to be the most hazardous turned out to be substantial improvements on the safety of methods used before recombinant DNA techniques were developed. This is because our most feared disease organisms evolved with us. Their ability to cause disease depends on their knowledge of us, if I can be forgiven the anthropomorphism. Thus for example a toxin-producing bacterium can generally be a pathogen only if it knows how to deliver its toxin to the right place. For a bacterium that lives in the gut, this can mean the ability to attach to and proliferate in the area that the toxin affects. Cloning the toxin gene into a laboratory bacterial strain does not turn the laboratory bacterium into a pathogen. The laboratory strain cannot survive in the gut, much less proliferate and deliver the toxin to the appropriate target cells. So the safest way to analyze toxin genes is in fact to clone them in laboratory bacterial strains.

THE CONTROVERSY OVER THE SAFETY of recombinant DNA has subsided, but only to some extent. It is now generally agreed that the initial guidelines for recombinant DNA research were unnecessarily stringent and that much more time and money were expended on the construction and equipping of special facilities and the construction of special "safe" organisms than the real dangers justified. Early in their development, the guidelines were cumbersome and the administrative work of complying with them was excessive. Research was delayed in many cases, although the delays seemed much more burdensome while endured than they appear in retrospect. There were efforts to convert the guidelines into regulations through legislation at the national level, but by good fortune and the efforts of several prominent biologists, such efforts failed. And the NIH Recombinant DNA Advisory Committee proved itself able to absorb accumulating information, gradually relaxing the guidelines as the results of risk-assessment studies became available. An unfortunate consequence of the controversy is that its intensity and abrasiveness obscured and distorted the legitimate, responsible concerns of the original group of scientists. Many admit that they would not speak out again under similar circumstances. It is indeed unfortunate that this first effort to foresee harmful outcomes of well-intentioned experiments became so embattled. What we have understood from this experience is the difficulty for us as an open society of

developing effective ways of venturing cautiously into the unknown, neither minimizing nor exaggerating the dangers, neither immobilizing ourselves with restrictive regulations nor proceeding without care. And the task is far from done; indeed, current applications of recombinant DNA research are again in the news, again under fire.

Recombinant DNA techniques have begun to come of age. We are witnessing the emergence of the first efforts to put the results of the knowledge gained through these techniques to work in both medicine and agriculture. Such practical applications raise issues that have not previously been considered. The applications now under discussion involve the introduction of genetically engineered organisms into the environment and efforts to transfer cloned genes between species to improve the value of agriculturally important animals. During the past year or two, much of the Recombinant DNA Advisory Committee's effort, as well as that of similar committees that have been formed in other government agencies such as the Environmental Protection Agency and the Department of Agriculture, has gone into the difficult task of divising suitable ways of assessing the chance that a genetically altered organism will have unexpected properties when released into the environment. I believe that the various committees have been and will be effective in this role. The open, prior discussion of new types of technological developments is useful. In some sense, it is what the original signers of the Berg letter had in mind, a concerted, ongoing effort to think through in advance the safest way to do a new type of experiment. But this view is far from universal and once again we find ourselves in the midst of public controversy over potential hazards, unable to agree on a prudent course. Some would forbid all medical and agricultural applications as too risky, whereas others believe that the risks are negligible.

The imminence of concrete applications in both agriculture and medicine has also prompted discussion of their ethical implications. Some view the possible applications of recombinant DNA techniques as so novel that they confront us with unprecedented ethical decisions and moral choices. It is the ability to control our genetic destiny, as well as that of other organisms, that is regarded as disquietingly new, but I think that this is perhaps because we forget how much genetic manipulation we already do. And perhaps, too, because we do not stop to consider the extent to which organisms, all organisms, influence each other genetically, altering each other's evolutionary fates.

THE DOMESTICATION OF PLANTS AND ANIMALS involved profound genetic changes; it was an evolutionary process. The plants and animals that evolved with us are very different from their wild ancestors. Corn provides a dramatic example of the rapidity with which a plant can evolve under the influence of another organism, in this case *Homo sapiens*. Today's familiar corn plant is very different from its closest living wild relative, the teosinte plant. Teosinte is a grass; it has narrow leaves, grows in clumps, and produces seed in the way other grasses do. Our modern corn plant has a single

robust stalk and carries its many hundreds of seeds, the corn kernels, on bulky ears that grow out of the stalk halfway up the plant. Yet these plants are so closely related that they form fertile hybrids. Furthermore, certain DNA sequences in their chromosomes are sufficiently similar that we estimate that the two species diverged only about 10,000 years ago, when human beings first appeared in their habitat. In that short span of time, the plant has changed genetically from just another wild grass to one of the most productive food plants in existence. Let me give you some idea of how short an evolutionary time span this is. We know from paleobotanical evidence that ferns have looked much like they do today for 50 to 100 million years. A million and a half years ago, our predecessor *Homo erectus* wandered the earth. Neanderthal man, a subspecies of our own species *Homo sapiens,* dates back about 150,000 years. Corn evolved in an evolutionary instant.

How did this happen? We can't go back 10,000 years and know exactly, of course, but we can make some good guesses based on what we have accomplished in plant breeding in the past few centuries. Contemporary breeding involves making controlled crosses between individuals with desirable characteristics and then selecting the best progeny for further propagation. Our ancestors undoubtedly began their breeding efforts simply by selecting certain offspring of plants and animals and discarding others. This is selective propagation, and it works because it automatically restricts the mating population to the selected individuals. Why do these procedures make organisms change or evolve? They don't, really. All they do is select for further reproduction those organisms that already have important genetic changes. The genetic material, the genes of all organisms, is in a constant state of flux. The more we learn about genes at the molecular level, the more we appreciate the extent to which chromosomes and genes are continuously changing in both their structure and their relationships to each other. This genetic instability is the ever-renewable source of future change, of new directions in the evolution of organisms. The breeder culls, picking certain directions of change over others. The selection process works because it is the nature of living organisms to change. Our objectives are, of course, to select out those plants or animals whose characteristics best suit us. Corn is one of our most dramatic success stories. We suspect that corn is almost entirely the product of human intervention.

Human beings and their corn plants are interdependent. We depend on corn for food and it depends on us for survival. The corn plant cannot survive without human beings because its seeds, the kernels, are so firmly attached to the ears that they do not fall off. In technical terms, the plant has no natural dispersal mechanism. Human beings serve the corn plant by removing the kernels from the ears and dispersing them to farmers, who in turn plant and tend the corn, ensuring its survival. Such mutual interdependence of organisms is by no means a human invention. It is evident everywhere in the living world. For example, many plants are completely dependent on insects for pollination, the step in the reproductive cycle that initiates the development of the seeds that grow into the next generation of plants.

Such mutual interdependence develops over a long period of time. We have come to call the process coevolution. Coevolved organisms are often so interdependent that the extinction of one organism assures the extinction of another. In one of his natural history essays, Steven J. Gould tells the poignant story of a coevolved pair of organisms, one of which became extinct, leaving the other behind to live out an uncomfortable existence. While wandering on the beach in Bermuda as a student, Gould noticed some hermit crabs that seemed, for the most part, to be living in uncomfortably small snail shells. Just a few of them had shells of a suitable size. All of the larger, more commodious shells, what few there were of them, turned out to be fossil shells. It appears that the snail species that this particular hermit crab coevolved with had become extinct, leaving only small-shelled snails. The poor hermit crab was condemned to cramped quarters for the rest of its existence. Only a few of the crabs, those lucky enough to find a fossil snail shell, would ever have a comfortable house. And in our contemporary jargon, the fossil shells are surely a nonrenewable resource.[5]

5. See Stephen J. Gould, "Nature's Odd Couples," *The Panda's Thumb* (New York: Norton, 1980), pp. 278–88.

MY OBJECTIVE IN ALL OF THIS is to illustrate two important points. The first is that change is fundamental to living organisms. The second is that organisms are intimately interconnected and participate in each others' evolution. Life is our planet's ever-changing, ongoing experiment in which success is never a sure thing (a hermit crab cannot even count on a decent housing subsidy). We human beings participate in interdependent relationships, just as do other species. We, like other organisms, exert our influence on the evolution of plants and other animals and are in turn influenced. Although recombinant DNA techniques extend our ability to influence our biological environment, the exercise of such influence is by no means novel. Our success in breeding plants and animals has improved in the past few centuries as we have gradually come to understand more and more about heredity and genetics, but we have been in the breeding business, the business of genetic manipulation, for a few thousand years.

Nonetheless, in certain respects recombinant DNA technology has dramatically extended our ability to influence our biological environment. It allows us to transfer genes between very different organisms, not only to learn how the genes work but to develop genetic systems to do specific tasks. We have already put the humble bacterium *E. coli* to work making products of medical value, such as growth hormone, interferon, and insulin. There is much work yet to be done for which recombinant DNA techniques should be ideally suited. We can begin to look forward to a time when we will be able to reach across the genetic barriers that have hitherto stopped breeders to introduce genes from diverse sources that will enhance the growth rate or food value of both plants and animals. Of particular importance is the possibility that we will be able to introduce genes to do some of the things we now do with fertilizers, herbicides, and pesticides.

Although I have argued that recombinant DNA techniques are

continuous with previous genetic technologies, I do not mean to imply that the application of recombinant DNA technology in agriculture and medicine will be without ethical dilemmas. It is simply that the kinds of ethical questions we are likely to confront are ones we are already grappling with. As with any human technology, there exists the possibility of misuse. We are, as a society, committed to the beneficial applications of technology. We struggle to keep our commitment, difficult though that struggle might seem on occasion. There is nothing about recombinant DNA technology that calls that commitment into question. In medicine, our overall goal is to ameliorate suffering and cure disease. Gene therapy is just another of many recent developments, not unlike organ transplantation and sophisticated drug therapies. It holds the promise of eradicating some hereditary diseases forever. This has been viewed as quite novel, but it is not, I think, altogether different from our ability to eradicate smallpox. In that case we eliminated an organism by eliminating ourselves as its host; by gene therapy we might be able to eliminate a gene defect. I can foresee that gene therapy will confront us with choices. I can anticipate that gene therapy, like other medical treatments, will not be invariably successful. The decision to resort to such therapy may well be a difficult one. But that is not different from many of the difficult choices that modern medicine confronts us with today. We must continue to seek to balance the chances of cure against the chances of failure and more suffering. What I believe is most important to appreciate is that, although recombinant DNA technology extends our ability to shape ourselves and our biological environment, we already do so extensively, if not always wisely.

What I do find both extraordinary and deeply disquieting is the emergence of a concerted campaign to prevent research leading to practical applications of recombinant DNA in agriculture and medicine. This is essentially the personal crusade of one individual, Jeremy Rifkin, who believes that there is something intrinsically immoral about research involving recombinant DNA and gene transfer. And he is attempting to impose his conviction on scientists, on universities, on the government, and on industrial concerns. Through a variety of legal maneuvers, he has slowed or stopped field testing of agriculturally useful organisms developed with recombinant DNA techniques. He further requested that the Recombinant DNA Advisory Committee amend the guidelines governing recombinant DNA research not only to prohibit but to declare immoral and unethical all transfer of genetic traits between mammalian species and from any mammalian species into humans. Rifkin believes that the transfer of a single gene represents "a fundamental assault on the principle of species integrity." He would have had the committee condemn such experimentation as "a gross and unconscionable violation of our telos as a species." He further requested that the NIH extend this condemnation to experiments involving all biological organisms.[6]

Although these notions have little scientific validity, they have a strong emotional appeal because of our growing awareness that we have misused many technologies. The term "telos" means "ultimate

6. Quotations from the *Federal Register*, 20 September 1984, pp. 37016–17.

end or aim." The fossil record tells us that species arise, persist for a time, and become extinct. Species have an ultimate fate, but it is we who invent and ascribe purpose. Genetic and molecular experiments show us that genes and chromosomes are in constant flux, that organisms change, and that species are man-made categories in the continuum of life. The principle of "species integrity," the notion that there is a fixed, unchangeable, and inviolable genetic structure is Rifkin's invention. Yet we are especially vulnerable right now to critics of science and technology. In our own country and throughout the world, we are being forced to confront the consequences of our rapid industrial and technological development. It is perhaps easiest and even traditional to blame scientists, those who acquire the knowledge that is used and misused. Our myths are full of fall guys. Eve took the blame when Adam ate the fruit of the tree of knowledge. For the gift of fire, Prometheus was chained to a rock and left for eagles to consume alive. Such myths are strong stuff: to be curious, to open Pandora's box, is to open a can of worms. Such myths make manifest our deeply ambiguous feelings about the acquisition of knowledge. Ignorance, we say, is bliss. We would prefer to evade responsibility for distinguishing between good and bad applications, the ethical and the unethical uses of knowledge.

But the answer to arson is surely not to declare all use of fire immoral. The answer is to define what arson is and to punish individuals who wantonly set fires, so that we might continue to use fire to cook food and keep warm. And so it is with recombinant DNA and gene transfer technology. Our distress over the disasters we have caused with other technologies tempts us to think that if we did not have certain kinds of knowledge, we would not be in the bind we are in. Indeed, to use knowledge wisely, responsibly, and with compassion is infinitely more difficult than to acquire it. But to declare the acquisition of knowledge outside the bounds of approved human activity, to declare it immoral, is truly to discard both baby and bath water. It is to discard the possibility of using biotechnology to help human beings born with crippling genetic disorders. And perhaps of greater importance in the overall scheme of things, it is to discard the possibility of using our knowledge of genes and organisms to achieve a better balance between human beings and all the other creatures on our populous planet.

Acknowledgment

FOR WILLIAM WASSERSTROM

In writing this article for the *Syracuse Scholar,* I acknowledge a special debt to the late William Wasserstrom, one of the most important of my professors at Syracuse University twenty years ago. From his undergraduate short story course, W. W. invited me to participate in several of his graduate seminars, all extraordinary exercises in his rich, deep, and passionate way of seeing literature, reading life. Although I became a scientist, he reminded me repeatedly in subsequent years of his conviction that I should be communicating more than just experimental results and to more people than just my scientific peers. In particular, and beginning from the time of his first efforts to organize the *Scholar,* W. W. sought my participation in this special venture. It took me some years to fulfill his expectations. It seemed that I was always too busy doing experiments and later being a participant in the business of regulating recombinant DNA research. I am grateful, then, that the Phi Beta Kappa Visiting Scholar Program provided me with the impetus both to reflect on what it was all about and then to put my thoughts in a form not altogether unsuitable for *Syracuse Scholar.* I am grateful, too, for W. W.'s editorial comments on the manuscript and pleased to acknowledge his deeper participation as teacher and friend.