

## The recombinant DNA controversy: Twenty years later

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February 24–26 of this year was the 20th anniversary of the Asilomar Conference that considered the public health implications of what was then a new genetic technology—recombinant DNA. Looking back now, this unique conference marked the beginning of an exceptional era for science and for the public discussion of science policy—one that continues unabated to this day. This year alone saw a scientist turn back \$614,000 in research grants, as a measure of what he perceives as the possible misdirections of current molecular genetics, and a call, by religious leaders representing 80 different faiths and denominations, opposing “the patenting of genetically engineered animals and human genes, cells, and organs.” This 20th anniversary is then an important opportunity to reflect on the history of that occasion and its ramifications.

What events led to the conference? Eight months earlier, in July 1974, a call for a voluntary moratorium on certain scientific experiments using the emerging recombinant DNA technology startled the world-wide scientific community (1). This unprecedented action by a group of American scientists echoed reservations expressed at a Gordon Conference on nucleic acids the summer before (2). Both groups acknowledged that the new technology created extraordinary novel avenues for genetics and could ultimately provide exceptional opportunities for medicine, agriculture, and industry. Nevertheless, the scientists were concerned that unfettered pursuit of this research might engender unforeseen and damaging consequences for human health and the Earth’s ecosystems. In spite of widespread consternation among many scientists about the proscriptions, the validity of the concerns, and the manner in which they were announced, the moratorium was universally observed. One goal of the moratorium was to provide time for a conference that would evaluate the state of the new technology and the risks, if any, associated with it.

That conference, held at the Asilomar Conference Center on California’s Monterey peninsula, included scientists from throughout the world, lawyers, members of the press, and government officials. One aim of the meeting was to consider whether to lift the voluntary moratorium and, if so, under what conditions the research could proceed safely. Although there were few data on which to base a scientifically defensible judgment, the conference concluded, not without outspoken opposition from some of its more notable participants, that recombinant DNA research should proceed but under strict guidelines (3). Such guidelines were subsequently promulgated by the National Institutes of Health and comparable bodies in other countries (4).

The primary motivation for the prompt actions taken by scientists and governments in the period 1973–1976 was to protect laboratory personnel, the general public, and the environment from any hazards that might be directly generated by the experiments. In particular, there were speculations that normally innocuous microbes could be changed into human pathogens by introducing genes that rendered them resistant to then-available antibiotics, or enabled them to produce dangerous toxins, or transformed them into cancer-

causing agents. The uncertainties stimulated a sometimes turbulent debate. Public fear was fanned by the popularity of “The Andromeda Strain” and the myriad “what ifs” floated by both serious and demagogic commentators. Also plaguing the debate over the necessity for or adequacy of the measures proposed to minimize imagined risks was the ignorance, even in the scientific community, about the properties of cells and viruses containing foreign genes, including whether such cells and viruses posed any risk at all. Some scientists, and public officials as well, were certain that recombinant DNA research was flirting with disaster and that lifting the moratorium was a blunder. Others, reflecting their intuition and expertise, argued that such cells, viruses, and recombinant DNAs posed no risk at all. The overwhelming assessment today is that the latter view was correct. Literally millions of experiments, many even inconceivable in 1975, have been carried out in the last 20 years without incident. No documented hazard to public health has been attributable to the applications of recombinant DNA technology. Moreover, the concern of some that moving DNA among species would breach customary breeding barriers and have profound effects on natural evolutionary processes has substantially disappeared as the science revealed that such exchanges occur in nature.

The use of the recombinant DNA technology now dominates research in biology. It has altered both the way questions are formulated and the way solutions are sought. The isolation of genes from any organism on our planet, alive or dead, is now routine. Furthermore, the construction of new variants of genes, chromosomes, and viruses is standard practice in research laboratories, as is the introduction of genes into microbes, plants, and experimental animals. Equally profound is the influence it has had in many related fields. Even a brief look at journals in such diverse fields as chemistry, evolutionary biology, paleontology, anthropology, linguistics, psychology, medicine, plant science, and surprisingly enough, forensics, information theory, and computer science shows the pervasive influence of this new paradigm.

But the most profound consequence of the recombinant DNA technology has been our increased knowledge of fundamental life processes. No longer is the gene an abstract notion, nor is it as enigmatic as interstellar dark matter or black holes. Genes, and chromosomes of which they are a part, are describable in precise chemical terms. Even more significantly, genes can be synthesized in test tubes, manipulated, and reintroduced into the cells of living organisms, enabling us to link genes with specific physiological functions. An even abbreviated enumeration of the extraordinary advances stemming from the recombinant and associated technologies is beyond the scope of this commentary, but a few brief examples can provide a sense of the breadth of the research’s implications.

(i) The ability to isolate genes readily and to determine their chemical structure unexpectedly revealed that genetic messages—the genes—of vertebrates, including humans are filled with interruptions, a feature that is largely missing from genes of “simpler” organisms. These interruptions must be edited out before the genetic messages make sense, and because the editing process can occur in a variety of ways, many genes encode multiple functions. Consequently, the amount of ge-

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netic information contained in mammalian genomes is considerably greater than previously thought.

(ii) Complex multicellular organisms develop from seemingly simple beginnings, a single fertilized egg, by an orderly, genetically preordained process. The recombinant DNA and associated technologies allow the identification of genes controlling the establishment of the embryo's body plan and the subsequent elaboration of fully functional newborns. Furthermore, whether recovered from worms, flies, mice, or humans, genes governing the formation of the skeleton, the brain, and central nervous system are closely related in structure and function. Remarkably, even genes in yeast cells and mammals are similar and can replace one another functionally, although the last common ancestor of these organisms was likely to have existed 2 billion years ago or more.

(iii) For a long time, the events controlling the cell cycle, the transitions through which every cell passes when it divides into two, were mysterious. Today, the cell cycle is understood as a progression of molecular transformations, each rigorously controlled by genes and nutritional cues. Some signals drive the cells to multiply, while others act as brakes to proliferation. Disturbances in this delicate balance lead to either cell death or uncontrolled cellular multiplication. Remarkably, progress in understanding the mechanisms regulating cell division has been synergistic with major advances in cancer research. Indeed, cancer is best understood as a genetic disease arising from inherited or acquired mutations in normal genes—mutations that impair the machinery controlling cell proliferation. Some 100 such “cancer genes” (oncogenes and tumor-suppressor genes) have been identified, and the characterization of these, as well as of others that are likely to be discovered, offers the best hope for ultimately controlling cancer.

At the time of Asilomar, scientists optimistically predicted that the recombinant DNA methods would soon yield important products. In fact, such developments took longer than anticipated. The experiments were not as simple as was thought, and learning how to manipulate genes for useful purposes presented unexpected difficulties. Since the mid-1980s, however, the number of products has increased continually. Hormones, vaccines, therapeutic agents, and diagnostic tools are enhancing medical practice. The production and consumption of genetically engineered food plants are realities. A thriving biotechnology industry has created products, interesting jobs, and wealth for scientists and others. This intensive commercial activity and its intimate relation to science and research have also modified the relations between universities and industry. Some see the changes as beneficial, while others worry about an undesirable blurring of the traditionally different roles of universities and for-profit corporations. There are reasons to think that these complex new arrangements challenge our ability to maintain the openness and trust that are an essential assumption of fundamental research.

Frequently heard in the 1970s were criticisms of scientists for assuming leadership in formulating policies that were matters of public concern. This led some scientists to believe that the public debate itself was a great threat and that the fallout of claim and counterclaim would bring debilitating restrictions or even prohibitions on molecular biological research. In truth, many scientists grew impatient with the time-consuming, contentious debates. Yet the effort to inform the public also encouraged responsible public discussion, which succeeded in developing a consensus for the measured approach that many scientists supported. Restrictive national legislation was avoided, and in the long run, scientists benefitted from their forthrightness and prudent actions in the face of uncertainty.

One of these benefits was the willingness of government officials to adopt guidelines that were initially strict—they included proscriptions of certain lines of research and required

rigorous physical and biological containment—but allowed for timely relaxation as knowledge about the modified organisms accumulated. Consequently, after 20 years of research and risk assessment, most recombinant DNA experiments are, today, unregulated. Such experiments are now even part of the curriculum in good high schools. Members of Congress, a former Secretary of State, and the President of the United States have all experienced the excitement of recombinant DNA experiments. The fear of “Andromeda strains” has disappeared.

Just as the recombinant DNA techniques marked a paradigmatic shift in science, so could the approach to their regulation be more broadly adopted. For example, the regulation of environmental hazards is sometimes imposed only after materials are identified as dangerous through dramatic undesirable consequences. In other instances, strict regulations are left in place, even after a risk is known to be minimal. It would be more effective, especially in the face of uncertainty, to provide guidelines that will undergo timely changes in response to new scientific knowledge.

One felicitous outcome of the public debates on recombinant DNA is the increased public interest in biomedical research and molecular genetics. Genetics and its vocabulary is evident in the daily press and television news, and a good deal of the reporting is of high quality. On the positive side, widespread reporting stimulates knowledgeable public discussion of some of the social, political, and environmental issues that are and will be emerging from genetic medicine and the use of genetically modified plants in agriculture. On the down side is the tendency of reporters, sometimes with the aid of scientists, to overstate the findings or the immediacy of applications to human problems. This inclination is exacerbated by the very competitive situation with respect to grants and by interests in commercialization.

The public discussion of the implications of genetic manipulations initiated by scientists 20 years ago focused mainly on the novelty of the techniques themselves. Consequently, government agencies responsible for assuring the safety of foods, drugs, chemicals, and agricultural plants evaluated the products of recombinant DNA methods with special criteria. While some of these approaches have been changed, others have not. For example, there are less stringent requirements for the use of plants that have been modified by traditional breeding programs and are thus likely to contain unknown genetic changes than for those containing precise, known genetic alterations introduced by recombinant DNA methods. Widespread scientific illiteracy has perpetuated this scientifically indefensible legacy. Thus, while distinguished American chefs outspokenly oppose genetically engineered foods, they readily accept similar new products derived by less predictable but classical breeding methods.

An often voiced criticism of the early recombinant DNA discussions was the failure to consider the ethical and legal implications of genetic engineering of plants, animals, and humans. This choice of agenda was due neither to oversight nor unawareness; it was deliberate, partly because of lack of time at Asilomar and partly because it was premature to consider applications that were so speculative and certainly not imminent. In 1975, the principal and more urgent concern for those gathered at Asilomar was the possible effects of recombinant DNA on public health and safety.

Today, however, concern is focusing on ethical, legal, and environmental issues raised by the rapid pace of genetic advances and the increasing use of genetically modified animals and plants (5, 6). Discussion of these issues is confounded by the clash of some religious and philosophical beliefs with scientific goals and practical opportunities. For example, some genetically engineered animals are essential research tools for the investigation of human disease, while others produce valuable therapeutic agents; similarly, some genetically mod-

ified plants are vital for research, and others promise environmentally sound and economically attractive production of important materials. Yet a coalition of religious leaders now seeks to impede these developments by proposing a ban on patenting of human genes, cells, organs, and genetically modified organisms; their argument is that these are creations of God and not inventions of man. But scientists who synthesize genes by chemical techniques in their laboratories and recognize the near identity of genes between humans and other mammals, do not think of human DNA molecules as holy. Moreover, reaping the benefits of the new technologies requires commercial-sector participation, and that commitment may not occur without the protection of financial investments that patents provide. We shall, therefore, have to resolve the conflict between religious and scientific views about molecules and biological organisms, as well as the conflict between religious precepts and the moral imperative to do all we can to improve mankind's lot and relieve human suffering.

Another widely expressed concern stems from the growing ability to associate particular mutations or characteristic features in genes with disease manifestations or predispositions and the societal stresses, medical challenges, and personal anxieties expected to accompany their disclosure. Protection of individuals against new forms of discrimination (e.g., in employment opportunities and availability of adequate health and life insurance) will be needed to mitigate against these possibilities. In time, new therapies, now woefully lacking, will make the possibilities for early detection more attractive and desirable.

But perhaps the most deeply felt concern is that genetic research in general and the institution of broad-based genetic testing will spur a malevolent renewal of interest in eugenics. This view stems from the presumption that current attempts to perform gene therapy by modifying the genetic constitution of somatic cells—i.e., the nonreproductive cells of the body—a goal that most people find acceptable, will ultimately lead to

attempts to alter human germ-line genes—i.e., those passed on to future generations via sperm and eggs. There are technical reasons for believing that the value of such modifications for humans is questionable and, therefore, unnecessary. Indeed, many scientists agree that in the absence of any evidence of indisputable therapeutic utility and without absolute assurance of complete safety, attempts at human germ-line modification should not even be considered.

Inferring evil intent and calling for bans on genetic research denies the value of such research in fulfilling human dreams for improved health and the sustenance of a growing human population. Vigorous, informed public debate on all these issues should be fostered, as it is by the Ethical, Legal, and Social Implications (ELSI) Program of the Human Genome Project. The need for this debate is one reason to encourage widespread improvement in science education in American schools.

In retrospect, very few of those attending the Asilomar Conference foresaw the pervasive, complex, robust, and rich ramifications of recombinant DNA technology. Nor could most have predicted the pace at which fundamental understanding of biology has deepened. As with all changes in human thought and technological developments, we are left with new and unanticipated issues. And, as so often in the past, science, which itself is a uniquely human endeavor, is challenging traditional ideas and values.

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