Conflicts at the Science-Society Interface: The Recombinant DNA Controversy

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Introduction

In 1971 Paul Berg at Stanford began to plan an experiment involving the structure of SV40 virus. His plan was to insert genetic elements of the virus into a microorganism using new technical achievements being developed at the time. In discussing the experiment with colleagues it was pointed out that the virus had been reported possibly to infect humans. If the bacterium containing the viral genetic information were able to be released from the laboratory and infect an individual, a question arose as to whether intact virus might then be made which could infect the human host. Since the answer was not readily apparent, Berg did not do the experiment. Along with others doing similar research, he called together a group of scientists and lay people to discuss what the potential consequences of the experiments might be.

That meeting led to a large public controversy which became highly charged with scientific and intellectual excitement, as well as emotional and "gut-level" fears. Its impact on the public mind has been expressed in the pages of our daily comic strips, the covers of leading news media, attempts at legislation, and fictionalized TV movies. It is reasonable to conclude that few scientific issues have received such widespread public discussion or comment or raised such serious questions about scientific research: questions about who controls research, scientists or the general public; questions about whether certain types of basic research should be done at all.

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To some extent, much of the heat of this controversy has cooled: many of the issues have been resolved, albeit in an unsatisfactory fashion for many. Yet, I believe the controversy is still worthy of discussion as a paradigm of conflicts that occur at the interface of science and society. It may hopefully serve as a mechanism for enlightening us for dealing with other problems of this nature.

Recombinant DNA Technology

To understand the technological impact of the controversy, we must understand some of the basic science involved.[1] All living organisms carry out two basic types of activities: informational and functional. The gene or DNA is responsible for the informational part; protein is responsible for the functional part. Both substances are large bipolymers. Information in the DNA molecule is ultimately translated into functional information in protein; any changes in the structure of DNA ultimately result in changes in the function of a protein. In essence, a recombinant DNA experiment arranges to introduce a piece of foreign DNA into an organism's genetic make-up, causing that organism to express a biological activity not in its normal repertoire.

Two important discoveries provided the basis for the recombinant DNA technology.[2]The first was the discovery of bacterial plasmids, which are small extrachromosomal fragments of DNA. They can be isolated, modified in the laboratory, and reintroduced back into a cell. They often carry information coding for antibiotic resistance. Plasmid interchange frequently occurs in nature and is often responsible for the rapid dispersal of antibiotic resistance in natural populations in bacteria.

The second breakthrough was the discovery of restriction endonucleases, which are enzymes that recognize scientific sequences of DNA and break the chain at that point. Cleavage of the chain at this site leaves the DNA fragment with "sticky ends," that is, sections of single stranded DNA capable of interacting with cognate single stranded DNA on another molecule.

A typical recombinant DNA experiment is summarized as follows. Plasmids are isolated and cleaved with an endonuclease leaving it with "sticky ends." Foreign DNA is isolated and cleaved with the same nuclease, leaving it with a "sticky end" capable of interacting with that of the plasmid. These are then mixed and allowed to interact to form a chimera. The chimera is then closed up with an enzyme called a ligase and the chimeric plasmid is then introduced back into another bacterial cell. That cell will now hopefully express the new genetic information by the production of appropriate protein molecules.

Potential Benefits of Recombinant DNA Technology

What can one do with this technology? I think the implications are clear and profound and fall into areas of both fundamental science and technological benefits.[3]

Fractionation and Amplification of Complex Genomes

To illustrate the complexity of genetic systems, especially human genetic systems, let me make a comparison first made by Paul Berg several years ago.[4] The comparison involves the genetic capability of *E. coli*, a bacterium, with that of humans. All of the genetic information of *E. coli* is contained on a single chromosome which is a single molecule of double-stranded DNA. It consists of 3,000 to 4,000 genes of which a few thousand have now been identified.

By comparison, the human genome consists of 23 pairs of chromosomes of great complexity. A number of genetic loci have been identified, and more are being identified every day (the frequency has increased markedly with the advent of recombinant DNA techniques). But the distance between any two markers on a single human chromosome is such that two entire lengths of the *E. coli* chromosome could fit between them. This is about 6,000 to 8,000 unknown genes between any two positions. To understand this complexity, it is frequently necessary to transfer many of these genes into simpler organisms to study their expression independent of other

genes.

In addition to this complexity, many genes code for only a few copies of a given protein. To understand the function of a gene, it is necessary to understand the function of the protein coded for by the gene. To understand the function of the protein, it is frequently necessary to isolate it and study its properties and action. Recombinant DNA techniques provide a means of amplifying gene products many-fold to provide for their ready isolation and characterization.

Genetic Control

Recombinant DNA techniques provide the opportunity to study the expression of genes independent of their normal control mechanisms. This allows the chance to study the process of genetic regulation and the factors affecting it because we can remove the gene from the complex eucaryotic milieu into a simpler procaryotic system.

An example of this is the area of fetal development, in which a complex sequence of genes is turned off and on according to a precise and specific program. Recombinant techniques are allowing the isolation of some of this genetic information and should provide a means of following its regulation. Another example is the impact these techniques are having on the study of cancers, which are basically diseases of genetic regulation.

Potential to Create New Genetic Combinations Advantageous for Human Purposes

Recombinant DNA technologies provide the potential to create processes and methods for manufacturing a wide variety of agents useful for human purposes. A number of these new genetic combinations are already emerging from recombinant DNA technology. Let me cite a few realized and potential examples to illustrate this dimension.

A number of important drugs can now be manufactured by recombinant DNA techniques, some of which were impossible by other techniques. The manufacture of human insulin is an example. There may be a considerable shortage of beef and pig pancreas necessary to prepare insulin later in this decade, thereby creating a

shortage of animal insulin. Furthermore, many individuals suffer an allergic reaction to pig or beef insulin. By manufacturing human insulin directly by recombinant DNA technology we can provide a product of greater usefulness for many diabetic individuals.

Other possibilities in this area are the incorporation of genetic information for nitrogen fixation into plants, thereby reducing the need for nitrogeneous fertilizers; or transferring information for the ability to synthesize required amino acids into green crop plants, thereby creating more nutritious food stuffs. This list could grow to inordinate lengths and to some extent is limited only by the imagination of the researcher and his or her budget. These examples will suffice to illustrate the point.

Feasibility of Correcting Genetic Defects

A direct thrust of these technologies is the correction of genetic defects. At the present time, this is a relatively speculative area, although it is changing almost daily. The technology is sufficiently developed that questions necessary to solve the problems can be formulated in an accurate fashion. For example, a scheme for correcting sickle cell anemia has been outlined and the technology necessary to carry it out is being developed.[5]

Potential Problems with Recombinant DNA Technologies

Thus far, I have been a little like Miranda in *The Tempest* exclaiming the wonders of the "brave new world" of recombinant DNA technology. If there were only these wonders of the technology, there would never have been the controversy, so let me now discuss some of the potential and real dangers of the technology.

Creation of Potential Pathogens

Bernard Davis has referred to this as the "Andromeda Strain Scenario"[6] and it has received the most publicity. The problem arises from the fact that the bacterial organism used in most recombinant DNA work is *E. coli* which was originally isolated from a human intestine. While it can be occasionally pathogenic, it is generally

considered to be a human symbiont.

Fear arose over the consequences of incorporating certain information into this organism coupled with its accidental release from the laboratory. Consider, for example, the consequences of an *E. coli* with genes for botulism toxin incorporated into it. Potentially, one would have an organism capable of colonizing the human gut and making a substance toxic for humans. What would those consequences be?

I believe that Darwin gave us the answer to that question many years ago when he pointed out that for any organism to survive and reproduce in the real world outside of the laboratory, it must compete with its neighbors for nutrients and space. The present strain of *E. coli* is virtually incapable of surviving outside of the laboratory and it would not be able to compete in the intestine of an infected individual. This point is further supported by the mechanism whereby organisms like *E. coli* become established in the intestine. (They must be ingested in relatively large quantities.) Such an organism might make a laboratory worker sick if accidentally ingested; however, the organism should not colonize the worker's intestine so as to constitute a public health problem. In fairness, we must assume workers are able to assess risks of laboratory infections and are competent enough to take precautionary actions.

Potential for Creation of Weapons

I believe that the unintentional creation of a potent pathogen coupled with its widespread dispersal into the general population is relatively unlikely. However, its intentional creation and dispersal is another matter. Our understanding of disease processes is sufficiently great that we could intentionally devise a very nasty pathogen. Of all the potential problems posed by the recombinant DNA technology, I believe this one is the greatest. The recent Frank Herbert novel *The White Plague* provides an excellent fictionalized, albeit scientifically inaccurate, account of such a possibility.

How can we respond to the problem? Unfortunately, the technology is of sufficient simplicity that a truly satisfactory response is difficult, if not impossible. I can only envision some type of international control such as has been invoked to control biological

warfare, and hope for the best. Admittedly, this is a weak response, especially in light of our control of nuclear weapons, but it seems to be the best available.

Crossing of Evolutionary "Barriers"

There is a fundamental difference between all organisms found in nature. Bacteria are referred to as "procaryotic" organisms; all "higher" organisms are referred to as "eucaryotes." These terms express a major evolutionary difference in living organisms. Sinsheimer, Charaff, and others felt that there might truly be an evolutionary barrier between the two groups of organisms that should not be broken.[7] Furthermore, the consequences of breaking that barrier might be severe, although those consequences were not spelled out. It was implied that we might create an organism capable of taking over an environmental or evolutionary niche previously unavailable to it.

But does such an evolutionary barrier truly exist? Are procaryotes and eucaryotes truly in "genetic isolation" from each other? Are there no exchanges of genetic information between procaryotes and eucaryotes in nature? Nature tells us no, I believe. I point to the rumen as an example of eucaryotes and procaryotes living together where an exchange of genetic information must surely have occurred over the years of evolution. Furthermore, a major paradigm shaping modern biology holds that cell organelles in eucaryotic cells had their evolutionary origin in procaryotes that established a symbiotic relationship with pro-eucaryotic cells.

Davis has noted that indeed evolutionary barriers do exist.[8] But they exist to prevent wasteful matings, rather than to prevent monsters that might take over the Darwinian struggle.

Modifications of the "Essential" Human

Davis refers to this as the "Golem Scenario." It is indirectly related to one of the advantages I mentioned earlier, i.e., the direct intervention into the genetic machinery of humans. One can envision some type of "DNA stockroom" where one can go in and pick up a six-pack of high IQ, a little bit of curiosity, some docile behavior, and so forth for one's pending offspring.

The technology is slowly developing for a limited intervention for monogenetic traits, such as the correction of some types of genetic defects. However, most of the traits that people would like to intervene to change, such as intelligence or behavior, are at best polygenetic, if they have any genetic basis. These traits are difficult to define and understand, much less modify. If recombinant techniques were to be available, there is serious doubt as to whether they would be any more popular than are present day eugenic techniques.

Economic Aspects of Recombinant DNA

Recombinant DNA has now become big business. The price of a company's stock can vary in direct proportion to the number of molecular geneticists in its research stable. The economic implications are vast and raise serious ethical questions, many of which are unaddressed, much less resolved.[9] For example:

> —If an investigator develops a technological method while under federal sponsorship, is he or she then entitled to develop a company around that technology for economic profit?
>
> —Should research of this potential for social consequences be conducted in the secrecy of corporate laboratories where the major governing motive is corporate profits?
>
> —What sorts of risks are laboratory workers subject to, since the private sector of the research community is immune from federal guidelines regulating this research?

Other questions obviously come to mind as well; these only serve to sensitize the reader to the nature of the problem.

Lack of Maturity in Human Nature

Finally, we come to the point most eloquently expressed by Edwin Chargaff in his many writings.[10] This is the rather vague feeling that mankind is not capable of handling knowledge of this sort. The assertion is made that we need only look by analogy to the application of our knowledge of atomic structure to understand the basis of this concern. The concern is serious and profound. However,

like the potential for weapons usage, it is difficult to formulate an adequate or satisfactory response that acknowledges its serious nature.

In his play *The Physicists* Friedrich Durrenmatt's mathematician Mobius says: "what was once thought can never be unthought." We cannot put the genie of recombinant DNA back in the bottle, just as we have not been able to put the genie of atomic structure back. And I don't think we should put either back. A major theme of this paper has been the very significant present and future benefits of the recombinant DNA technology. It is a technology that holds the promise of great fundamental as well as practical knowledge for mankind. However, with knowledge comes responsibility. Somehow, we must develop the wisdom to control the application of knowledge.

Conclusions

Mary Williams, a philosopher in the Center for Science and Culture at Delaware, has developed an interesting analysis of the recombinant DNA controversy.[11] She pictures the proponents of the technique as allied philosophically with the utilitarians, while opponents seem to be building their arguments from a Kantian absolutism. While I find this analysis helpful, I think it misses a major motive of the scientists in the controversy. Many scientists are indeed seeking utilitarian benefits. However, many more are interested in the new knowledge made available by the technology; the technology is nothing more than a means of opening new windows into nature. To these individuals, it is the seeking of knowledge that is of paramount importance; an importance that frequently assumes Kantian overtones! However, despite the imperative aspect of this drive to understand nature, I know of few scientists who fit the Nathaniel Hawthorne or Mary Shelley model of the scientist who is willing to sacrifice everything for knowledge.

This is not to imply that I believe that all scientists are meticulous and careful in their work, or truly altruistic in their motives. Science is a part of the totality of human culture; consequently, scientists are

subject to the same foibles of human nature as all mankind. However, I do believe most scientists would reject any experiment which clearly posed humanistic or societal harm. Furthermore, I believe the history of the rcombinant DNA controversy supports this assertion, in that many of the potential dangers of the technologies were first pointed out by the scientists doing the research themselves.

The real danger of any science/society conflict comes not when the experiment threatens society physically (as with the creation of a pathogen) but rather when it threatens what are perceived as societal "values." Many see the recombinant DNA technology not so much as a threat to their health, but rather as a threat to perceived societal values. And this is the question that is so difficult to respond to.

A solution may lie in the model I alluded to in the title of this paper. The term "Science-Society Interface" is not meant to suggest the existence of two spheres — one labeled science, the other society. Rather, the term implies a single sphere labeled human culture, of which science and society are but two domains. Other domains might include the graphic arts, the performing arts, or the humanities. Each maintains its own integrity, but because of the construction of a sphere, each must come into contact with another, hence an interface. Each has its own separate values, hence conflicts can develop at the interface; the recombinant DNA controversy is typical of these conflicts. We must realize that science and society are not spheres of their own, but rather are components of the larger sphere of human culture. Somehow, we must identify the values of that sphere and allow those values to govern what happens at the interface of any of the domains.

ENDNOTES

[1]For more detail the reader is referred to any modern biology or molecular biology text; see, for example, James Watson, *The Molecular Biology of the Gene* (Menlo Park: W.A. Benjamin and Co., 1977).

[2]Stanley Cohen, "The Manipulation of Genes," *Sci. Amer.*, 233 (1975), 24-33.

[3]See, for example, *Research with Recombinant DNA* (Washington, D.C.: National Academy of Sciences Forum, 1977).

[4]Paul Berg, in *Research with Recombinant DNA*, pp. 62-73.

[5]David Baltimore, in *Research with Recombinant DNA*, pp. 237-46.

[6]Bernard Davis, "The Recombinant DNA Scenarios: Andromeda Strain, Chimera and Golem," *Amer. Sci.*, 65 (1977), 547-613.

[7]Robert Sinsheimer, "On Coupling Inquiry and Wisdom," *Fed. Proc.*, 35 (1976), 2540-42; "An Evolutionary Perspective for Genetic Engineering," *New Scientist*, 20 Jan. 1977, p. 150; and Edwin Chargaff, "On the Dangers of Genetic Meddling," *Science*, 192 (1976), 938.

[8]Davis, pp. 547-613.

[9]Nicholas Wade, "Recombinant DNA: Warming Up for the Big Pay Off," *Science*, 206 (1979), 663-65.

[10]See for example: Edwin Chargaff, "Bitter Fruits from the Tree of Knowledge: Remarks on the Current Revulsion from Science," *Persp. Biol. and Med.*, 16 (1973), 486-502; and "Voices in the Labyrinth: Dialogues Around the Study of Nature," *Persp. Biol. and Med.*, 18 (1973), 313-30.

[11]Mary Williams, "Ethical Theories Underlying the Recombinant DNA Controversy," in *Recombinant DNA: Science, Ethics, and Politics*, ed. John Richards (New York: Academic Press, 1978).