ETHICAL ISSUES IN RECOMBINANT DNA RESEARCH

Claude A. Villee, Ph.D.

Department of Biological Chemistry and
Laboratory of Human Reproduction and
Reproductive Biology, Harvard Medical
School, Boston, Massachusetts 02115.

Seldom in the history of science has any new field of research been subjected to as much public debate as has this area termed recombinant DNA. The question reached public consciousness when some of the molecular biologists working in the field became anxious over the possibility that their experiments might have dangerous and undesirable results. At meetings in New Hampshire in the summer of 1973, at MIT in April of 1974 and at Asilomar here in California in February, 1975 this group proposed a moratorium on certain kinds of recombinant DNA research. Their proposals for a voluntary ban on experiments involving animal tumor viruses, those increasing drug resistance and those increasing toxicity were published in Science and in Nature. After the Asilomar meeting they pressed the National Institutes of Health to establish regulations for safe levels of physical and biological containment that should be required for different types of recombinant DNA experiments.

The aim of these meetings was to allay public fears about their work, but of course they only fanned public fears tremendously. Newspapers and magazines ran stories with scary headlines and some made exaggerated prophesies of doom. Within two months Senator Kennedy entered the scene and opened hearings on the new genetics to determine whether new legislation was needed to deal with the problem.

The arguments presented against recombinant DNA research fell into four categories. (1) Health Hazards: It is argued that the research involves hazards such

as the possible inadvertent creation of new pathogens or new biological niches for DNAs that code for toxins or oncogenic viruses. It is feared that the new pathogenic virus or bacterium will escape somehow from the laboratory and kill millions of humans. (2) Species Barriers: It is argued that humankind should not exploit the power of crossing species barriers between eukaryotic and prokaryotic organisms and thus take into its own hands the future of evolution on the planet. (3) Genetic Engineering: It is alleged that recombinant DNA techniques will eventually lead to baneful forms of genetic engineering whereby the solution to social problems will be sought in the alteration of the human genome, and, (4) Misplaced Priorities: Opponents argue that the benefits of the research can be obtained through less risky procedures and that proponents are asking the wrong questions and misplacing national priorities. They claim that even if the research would provide clues to the cancer problem this places emphasis on the individual and not on the social causes of cancer. The opponents argue that money allocated to this research would be better spent in reducing the levels of environmental carcinogens.

It is now becoming even clearer that these underlying anxieties are not warranted and we should take great care not to waste millions of dollars in unwarranted restrictions on this sort of research. Some of the concerned laymen in this field have been misled into believing that there is sharp disagreement among experts regarding the hazards of research in this field. The experts are in fact those who are specialists in epidemiology and infectious disease and these experts do not perceive the hazards as serious. The record

of work over many decades with dangerous organisms shows that the alarm exhibited by some scientists who are not experts in the field is not justified. One certain fact is that no known untoward event has resulted from recombinant DNA research.

Let's consider the problem of genetic engineering first. Genetic engineering began nearly half a century ago when workers at the Rockefeller Institute were able to modify in the test tube the genetic characteristics of the pneumococcus, the bacterium that causes lobar pneumonia. This ultimately led, in 1944, to the tremendously important demonstration by Avery and his colleagues that DNA rather than protein is the carrier of heredity. In succeeding years new techniques have made it possible to transfer in the laboratory genes from one kind of living thing to another kind, but it is totally misleading to state that scientists are now able to create new forms of life. What can be done is to introduce a few genes into fairly simple microbes, genes that were derived from other microbes, from plants or from animals, including human beings. That such genetic combination is possible has created both hope that the techniques can be used for beneficial purposes and fear that it might generate new diseases or lead to the manipulation of human nature. It cannot be argued, however, that this is contrary to the ways of nature because such genetic exchanges occur frequently under natural conditions. In nature harmless bacteria may incorporate gene fragments from other bacteria and become able to produce toxins, to resist antibiotics and to cause cancer in plants. On the other hand, virulent bacteria can lose the genes that make them dangerous and become harmless. It seems likely that bacteria can incorporate DNA fragments from the animals or plants in which they are residing. Thus gene exchange occurs quite widely in nature and it would seem quite

ethical to carry out gene exchanges experimentally under controlled conditions. Although human genes can be incorporated into bacteria, changing human nature by genetic engineering seems incredibly unlikely, if not impossible. It may ultimately be possible to correct a few genetic maladies, but it is much more difficult to insert DNA into human cells than into a bacterial cell.

The likelihood that this type of research will produce strains of microbes that will start new epidemics or cause a new form of disease also is very unlikely. Everywhere in nature are untold billions of microbes constantly undergoing genetic changes. Yet only a very few of these cause disease and even these can infect human beings only when conditions are just right. It seems unlikely that genetic recombination in the laboratory can create bacteria or viruses that are more virulent than those that are continually being produced by natural processes. The potential benefits of recombinant DNA research are considerable and its dangers are purely hypothetical.

Early this year, a research team at the University of California, San Francisco, directed by Drs. William Rutter and Howard Goodman, was able to transfer the gene for insulin from a rat into the bacterium Escherichia coli. Although that part of the experiment was successful the new host is not making insulin. The Rutter group did not actually isolate the DNA gene for insulin, but prepared some messenger RNA from cells of the islets of Langerhans which make insulin in the pancreas. They partially purified the messenger RNA by density gradient centrifugation and then, using reverse transcriptase,

made DNA copies of the messenger RNA. These DNA copies were hooked to a plasmid, a circular DNA molecule carrying a few genes that the bacterium can maintain and duplicate in addition to its normal chromosome. These plasmids were then put into cells of Escherichia coli and sorted from unchanged bacteria. Further experiments showed that these cells contain the entire intact DNA insulin sequence or parts of it. Although the bacterial host has not yet been fooled into making insulin from the rat genes, it appears that this may be due to the lack of some control switch needed to turn on the transcription of the insulin gene in the bacterium. These experiments have been hailed as showing the possible benefits of recombinant DNA research and their possible practical applications.

It now appears that the potential risks of recombinant DNA research were greatly overestimated when the issue was first raised. The present NIH guidelines and rules for doing recombinant DNA research require a great deal of extra paper work which seriously impedes investigators doing the research and discourages others from entering the field.

There are heartening signs that some of the scientists who originally had expressed greatest concern over possible risks involved in this research have come to the conclusion that the risks are minimal - much less than perceived earlier. The legislation proposed by Senator Kennedy to establish a national regulatory commission to govern recombinant DNA research was dropped last month and regulation of the research remains within the National Institutes of Health.

The NIH guidelines which govern all federally supported research established a set of conditions for the physical and biological containment of potentially dangerous organisms with the degree of containment required in an experiment appropriate to its likelihood of producing a harmful product. Four levels of physical containment were established, P_1 through P_4. The latter is equivalent to work with dangerous infectious diseases or agents of chemical warfare where no escape of contaminated air, wastes or untreated materials is permitted. There is only one P_4 laboratory at present in the United States and it is in a trailer on the NIH campus in Bethesda. There are plans to remodel some of the research facilities at Camp Dietrich at Frdderick, Maryland so that they will be available for P_4 recombinant DNA work.

Biological containment is achieved by using as a host for the recombinant DNA a strain of Escherichia coli with several mutants that would cause it to die immediately if it escaped from the laboratory. Such a strain, produced by Roy Curtiss at the University of Alabama Medical Center, has several mutants which prevent it from manufacturing a protective outer membrane. It has defects in the genes that produce diaminopimelic acid, an ingredient of the membrane, and in the gene that produces colanic acid, a sticky substance that holds bacteria together. To the strain was added yet another defect, the inability to synthesize thymine, one of the components of DNA. Thus the bacterium is unable to survive unless it is supplied in the test tube with thymine, with diaminopimelic acid,

and with colanic acid.

Much in the news in the past year or so was an attempt by the mayor of Cambridge, Alfred Velluci, to halt DNA research within the city of Cambridge. Eventually a citizens' panel of eight people was appointed and this group, after extensive hearings, passed in February of this year an ordinance permitting recombinant DNA work to be resumed in Cambridge using standards that are slightly stricter than those advocated by NIH. An interesting report on this chapter of history was provided by one of the members of this citizens' panel, Dr. Sheldon Krimsky, Professor of Philosophy at Tufts University. In an article in Chemical and Engineering News of May 30, 1977 Dr. Krimsky explains how he saw the issues while serving on this review board and provides some of the reasoning behind the board's decision. This review board included a physician, a philosopher of science, a fuel oil distributor, a structural engineer, a clerk, a nurse, a social worker and a housewife. The review was conducted in an adversary format in which scientists were called upon to explain technical concepts and were cross-examined by their adversaries. At issue was whether proponents of the research must prove that it is safe beyond all reasonable doubt or whether the opponents must prove that if recombinant DNA research were undertaken there would be significant potential hazards. In its report this panel proclaimed that "Knowledge, whether for its own sake or for its potential benefits to humankind, cannot serve as a justification for introducing risks to

the public unless an informed citizenry is willing to accept those risks". Decisions regarding the appropriate course between the risks and benefits of potentially dangerous scientific inquiries must not be adjudicated within the inner circles of the scientific establishment. It should be noted that this citizens' committee began with a considerable suspicion of the ability of scientists to regulate themselves responsibly but ended up with a unanimous vote of confidence in the main features of the NIH guidelines. They did shift one set of experiments from P_2 to P_3, which seems like a highly technical decision which goes beyond the ability of a group of laymen to formulate general science policy.

On one side of the debate are microbiologists such as Bernard Davis and Harlyn Halvorson who believe that recombinant DNA research has very limited risks and that these are far outweighed by the potential benefits. These benefits are not only the possibility of treating human genetic diseases such as phenylketonuria or cystic fibrosis, but of gaining important new knowledge of fundamental biological mechanisms. These techniques would be most useful in mapping and sequencing the genes of animal cells such as the human and in reaching an understanding of the mechanisms by which genes are regulated. Each cell in a human being contains exactly the same set of genes as every other cell, but they differ in the patterns of which genes are turned on and transcribed and which remain silent. The problem of gene regulation is the key to one of the great unsolved problems in present day biology, that is the mechanism of cellular

differentiation, by which a fertilized egg develops into a differentiated organism composed of many cell types with unlike morphology, unlike functions, and unlike biochemical properties.

On the other side of the debate are chemists such as Erwin ~~Chengoff~~ Chargaff, Robert Sinsheimer and George Wald who argue that the entire field of recombinant DNA research should be abandoned. This is based in part on their perception of the alleged high risks of the research and in part on the philosophical argument that humans have no right to interfere with evolutionary forces and thus there are some areas of knowledge, such as splitting the atom and manipulating the gene, that are best left unknown and should not be explored. This concept of "forbidden knowledge" was rejected by scientists centuries ago and there seems no valid reason for raising it again now.

The American people, through their elected representatives in Congress, may decide that for safety it is necessary to declare a moratorium on DNA recombinant research or to pass restrictive regulations which limit such research to a very few institutions. Such policies, although paralyzing research in the United States, would not affect it in other countries. Recombinant DNA research can be carried out almost anywhere. It requires relatively simple laboratory equipment that is available in many places. It enables even poor countries to engage in sophisticated biological research that promises practical applications in medicine, agriculture and industry. It has both philosophical and scientific implications for the understanding of life.