THE ETHICS OF RECOMBIANT DNA RESEARCH. R. W. Newburgh, Oregon State University

Several years ago a group of scientists published a letter warning that certain experiments based on their research might best not be done. This involved the use of a technique now known as recombinant DNA. This letter stimulated much debate and eventually lead to the development of guidelines by the National Institutes of Health entitled, "Guidelines for Research Involving Recombinant--DNA Molecules".

The debate on the ethics of permitting research on recombinant DNA continues as evidence, for example, by this panel discussion. Whenever new scientific knowledge has the potential for both good and evil, debate results. In the case of recombinant DNA research the scientific community is split in regard to its justification which confuses the issue in the minds of the general public. The result is a negotiation between the scientific community and the public that is indeed complex.

A problem is how one informs the public and avoids sensationalism, and inexactitude. The actual problem may be that informing the public of the nature of science. In the area of biological research this means explaining that absolutes may not exist and that we are experimenting to demonstrate the limits of hypotheses. Included is a need to explain that differences of interpretation exist, based on questioning the methodology as well as the theory. While it is likely simplistic, the question of the ethics of recombinant DNA research is one of risk versus benefit.

For my part, I wish to divide my comments into three areas. One is related to successful biological research in the past that contained risk; another, a brief description of what is meant by recombinant DNA; and finally concrete examples of benefits.

Throughout history a thing that differentiates man from other beings is the ability to mold their environment to suit their own goals. An example of this that certainly may contain a risk is the use of vaccines. The benefit is the near elimination of the possibility of contracting certain diseases. The risk is that we cannot absolutely be sure that detrimental results will not occur sometime in the future, such as introduction of a virus with a vaccine that causes disease in the future.

If we were to examine the successes of medicine it is apparent that many of these involve the correcting of genetic diseases. An example of this is the use of insulin to correct diabetes.

In the area of evolution we have already been modifying natural processes by domesticating animals, and cultivating plants that result in an unnatural advantage to certain biological species. It is clear that the test of time indicates that such research was, and is, beneficial to the human.

The second area to be covered is that of what is meant by recombinant DNA research and speculation as to its use. Examination of the current means of reproduction indicates the existence of three levels. The first of these is sexual and is limited to members of the same species. The second is asexual and includes such things as transformation and transduction, and requires considerable DNA homology. The third is recombinant DNA. This does not require the same species as sexual reproduction does nor considerable DNA homology as in asexual reproduction. It is based on the discovery of restriction enzymes, the means of splicing together DNA segments, the use of plasmids, and the ability to put these new DNA segments contained in plasmids into an organism such as the bacterium, E. coli.

The term recombination is a genetic term. At the molecular level the recombination occurs between two strains such as a plasmid and a mammalian gene. The result is a mutant that contains the parental DNA molecules, as well as, segments of DNA from non-related species. This recombination can be accomplished in the test tube. The process in simplistic terms may be viewed as a vehicle and a passenger. The vehicles are plasmids or viruses and the passenger is the segment of DNA from another organism. Once the combination has been accomplished in the test tube this new recombined DNA is introduced into a host, most often a bacteria or mammalian cell culture line. In this kind of experiment only a minute fraction of the total genetic information of one individual is introduced into the total genetic information of the host. With this technique it is possible to study individual genes, to amplify these genes, to study the expression and control of genes, and to create new genetic combinations that are advantageous to mans use. It is speculated that benefits not only include a tool to advance knowledge

in the area of the structure and function of genes but in other areas. Some such benefits are the building of bacterial strains that can produce antibodies or hormones in large quantities at reduced cost, vaccine production, transplantation of the ability to fix nitrogen in non-legumenous plants, and the use of genes that produce hydrogen from water using sunlight--resulting in pollution free energy.

Research in the area of recombinant DNA while not that extensive has occurred and certain positive benefits have been demonstrated. It is some of these specifics that I now wish to convey to you using three examples.

One experiment involves hemoglobin DNA. The experiment consisted of isolating the messenger RNA, that is, the RNA that guides the synthesis of the protein, hemoglobin. Once the messenger RNA was isolated it was possible to introduce a DNA derived from it into a bacterium. This was accomplished by using an enzyme reverse transcriptase, creating a complimentary DNA (cDNA) to the messenger RNA. Once this chemical was made and the RNA removed another enzyme, DNA polymerase was used to make a double stranded DNA. This DNA was linked in the test tube to a plasmid. This new DNA which contains the hemoglobin DNA was then used to transform an E. coli strain to one that contains the hemoglobin gene. In one experiment the hemoglobin messenger RNA from patients with sickle cell anemia was used to make the complimentary DNA. With these systems it is now possible to study structural and biological differences between the normal hemoglobin and the sickle cell hemoglobin genes.

In another experiment of recent date the gene for insulin was inserted. The purpose of the experiment was to study the structure of the insulin gene, its regulation and expression and to investigate the possibility of the synthesis of insulin by bacteria.

In the two experiments discussed all that was accomplished was to insert the gene for hemoglobin or insulin into a bacterium. These bacteria were not able to initiate the synthesis of the products. In other words, the genes were in the bacteria but were not expressed. The bacteria could replicate and the one for insulin was replicated but not expressed. Recently another group used the gene for somatostatin, a hormone that inhibits the secretion of the pituitary gland. These workers synthesized copies of

the gene and inserted the cDNA into a strain of E. coli. In this experiment the bacteria made the hormone, somatostatin. This hormone can be isolated from sheep brains but to get 5 mg. requires 500,000 sheep brains. It took only two gallons of bacteria culture to get the same 5 mg. This is a real breakthrough.

The projections for the worlds food picture are rather grim. Although we have abudant agricultural productivity in the United States for our needs, this is not true world=wide. Increasing pressures exist to produce more food at a time when prime agricultural land is removed from production due to urban growth, water shortages are a critical problem, as is the limitation of energy. Energy requirements for production of fertilizers are significant. Many of the major crops such as cereals are plants that are unable to fix nitrogen. Even in nitrogen-fixing organisms energy supply is critical and we need better utilization of it.

In the plant kingdom, there are many possible experiments using recombinant DNA techniques that could result in better crops with more efficient use of energy. One area is that of plants that reproduce vegetatively such as potatoes. There is a system in some potatoes that produces a large amount of a particular protein. This occurs in a particular species that is small and undesirable to the consumer. However, if this gene can be put into a more desirable potato it means we can produce potatoes with a much increased protein content.

Another area in plant research is that the inclusion of the genes responsible for nitrogen fixation, nitrogenase genes, into non-nitrogen fixing bacteria or plants. Two groups have begun studies in this area. One group isolated the nitrogenase DNA from a nitrogen-fixing bacteria and constructed, using a plasmid, a E. coli strain containing nitrogenase genes. These strains were then transferred to mutants of Azotobacter lacking the nitrogenase genes.

The importance of this experiment is the demonstration that the nitrogen-fixing genes can be transferred to a non nitrogen-fixing organism, and then the plasmid containing the nitrogenase genes transferred back to a bacteria related to E. coli, Klebsiella pneumoniae, lacking the nitrogenase genes. In addition the plasmid could be

transferred to two unrelated species, Agrobacterium and Rhizobium.

The ability to transfer the nitrogen-fixing genes from Klebsiella to Azotobacter and for these genes to be transcribed has several important consequences: 1). Azotobacter glutamine synthetase can activate Klebsiella nif genes; 2). Klebsiella nif genes normally function only in an anaerobic environment, yet when transferred to the obligate aerobe, Azotobacter, they are expressed.

In this brief time I have tried to present some of the experiments that have been successful and are beneficial. The question that we seek an answer to is the ethics of recombinant DNA research. Recombinant DNA techniques are neither good nor bad per se as is true of any chemical. It is important to recognize that we cannot be certain that no harm will result in the distant future. There are few biological experiments that are any less risky. Certainly as scientists we are not likely to claim zero risk for a variety of experiments.

The problem is one of developing restrictions that minimize the risk while permitting expermentation that can benefit man. It is toward this end that after many hearings and continuing examination the NIH gudelines were developed. These guidelines establish a set of carefully controlled physical and biological containment conditions with containment in a particular experiment appropriate to its likelihood of producing a harmful product. There are four levels of physical containment, from P1 (equivelent to that in most routine bacteriology laboratories) up through increasing isolation from the environment until a containment equivelent to that used with dangerous infectious diseases or chemical warfare agents. In the latter, no escape of the contaminated air, water or untreated materials is permitted. Biological containment is achieved by using vectors or hosts so crippled by mutation that the organisms bearing recombinant DNA should be incapable of surviving outside the laboratory.

I would leave you with this conclusion. In the area of recombinant DNA scientists have shown considerable wisdom in trying to regulate the use of a scientific discovery. As always a problem is that the progress of science has not kept pace with the wisdom of ~~bums~~ humans to regulate themselves. We cannot say with certainty that our efforts to

influence the weather, modify crops, or vaccinate populations do not equally carry risks. It all boils down to efforts to balance risk against benefit. In the area of recombinant DNA research there exists no concrete evidence thus far that we are unable to contain the product.

The larger question may be that of should we limit scientific research and if so, how do you do it? I might suggest that one should not limit scientific inquiry but when appropriate, limit the use of technology derived from science. It is this that has been accomplished in the case of recombinant DNA research.