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Splicing Life

The Social and Ethical Issues of Genetic Engineering with Human Beings

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

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Splicing Life

A Report on the Social and Ethical Issues of Genetic Engineering with Human Beings

November 1982

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

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November 16, 1982

The President
The White House
Washington, D.C. 20500

Dear Mr. President:

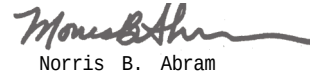
On behalf of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, I am pleased to transmit Splicing Life, our Report on the social and ethical issues of genetic engineering with human beings. This study, which was not within the Commission's legislative mandate, was prompted by a letter to your predecessor in July 1980 from Jewish, Catholic, and Protestant church associations. We embarked upon it, pursuant to §1802(a)(2) of our statute, at the urging of the President's Science Advisor.

Some people have suggested that developing the capability to splice human genes opens a Pandora's box, releasing mischief and harm far greater than the benefits for biomedical science. The Commission has not found this to be the case. The laboratory risks in this field have received careful attention from the scientific community and governmental bodies. The therapeutic applications now being planned are analogous to other forms of novel therapy and can be judged by general ethical standards and procedures, informed by an awareness of the particular risks and benefits that accompany each attempt at gene splicing.

Other, still hypothetical uses of gene splicing in human beings hold the potential for great benefit, such as heretofore impossible forms of treatment, as well as raising fundamental new ethical concerns. The Commission believes that it would be wise to have engaged in careful prior thought about steps such as treatments that can lead to heritable changes in human beings or those intended to enhance human abilities rather than simply correct deficiencies caused by well-defined genetic disorders. In light of a detailed analysis of the ethical and social issues of this subject--issues beyond the purview of existing mechanisms for Federal oversight--the Commission suggests several possible means, in the private as well as the public sector, through which these important matters can receive the necessary advance consideration.

The Commission is pleased to have had an opportunity to participate in the consideration of this issue of public concern and importance.

Respectfully,



Norris B. Abram
Chairman

President's Commission for the Study of Ethical Problems
in Medicine and Biomedical and Behavioral Research
Suite 555, 2000 K Street, N.W., Washington, DC 20006 (202) 653-8051

November 16, 1982

The Honorable George Bush
President
United States Senate
Washington, D.C. 20510

Dear Mr. President:

On behalf of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, I am pleased to transmit Splicing Life, our Report on the social and ethical issues of genetic engineering with human beings. This study, which was not within the Commission's legislative mandate, was prompted by a letter to the President in July 1980 from Jewish, Catholic, and Protestant church associations. We embarked upon it, pursuant to §1802(a)(2) of our statute, at the urging of the President's Science Advisor.

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November 16, 1982

The Honorable Thomas P. O'Neill, Jr.
Speaker
United States House of Representatives
Washington, D.C. 20515

Dear Mr. Speaker:

On behalf of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, I am pleased to transmit Splicing Life, our Report on the social and ethical issues of genetic engineering with human beings. This study, which was not within the Commission's legislative mandate, was prompted by a letter to the President in July 1980 from Jewish, Catholic, and Protestant church associations. We embarked upon it, pursuant to §1802(a)(2) of our statute, at the urging of the President's Science Advisor.

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Morris B. Abram
Chairman

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Summary of Conclusions and Recommendations

This Report addresses some of the major ethical and social implications of biologists' newly gained ability to manipulate—indeed, literally to splice together—the material that is responsible for the different forms of life on earth. The Commission began this study because of an urgent concern expressed to the President that no governmental body was "exercising adequate oversight or control, nor addressing the fundamental ethical questions" of these techniques, known collectively as "genetic engineering," particularly as they might be applied directly to human beings.[1]

When it first examined the question of governmental activity in this area, in the summer of 1980, the Commission found that this concern was well founded. Not only was no single agency charged with exploring this field but a number of the agencies that would have been expected to be involved with aspects of the subject were unprepared to deal with it, and the Federal interagency body set up to coordinate the field was not offering any continuing leadership. Two years later, possibly because of the Commission's attention, it appears the Federal agencies are more aware of, and are beginning to deal with, questions arising from genetic engineering, although their efforts primarily address the agricultural, industrial, and pharmaceutical uses of gene splicing rather than its diagnostic and therapeutic uses in human beings.[2]

The Commission did not restrict its examination of the subject to the responses of Federal agencies, however, because it perceived more important issues of substance behind the expressed concern about the lack of Federal oversight. The Commission chose, therefore, to address these underlying

[1] See Appendix B, pp. 95-96 *infra.*
[2] See Appendix C, pp. 97-106 *infra.*

issues, although certainly not to dispose of them. On many points, the Commission sees its contribution as stimulating thoughtful, long-term discussion rather than truncating such thinking with premature conclusions.

This study, undertaken within the time limitations imposed by the Commission's authorizing statute, is seen by the Commission as a first step in what ought to be a continuing public examination of the emerging questions posed by developments and prospects in the human applications of molecular genetics. First, the report attempts to clarify concerns about genetic engineering and to provide technical background intended to increase public understanding of the capabilities and potential of the technique. Next, it evaluates the issues of concern in ways meaningful for public policy, and analyses the need for an oversight mechanism.

To summarize, in this initial study the Commission finds that:

(1) Although public concern about gene splicing arose in the context of laboratory research with microorganisms, it seemed to reflect a deeper anxiety that work in this field might remake human beings, like Dr. Frankenstein's monster. These concerns seem to the Commission to be exaggerated. It is true that genetic engineering techniques are not only a powerful new tool for manipulating nature—including means of curing human illness—but also a challenge to some deeply held feelings about the meaning of being human and of family lineage. But as a product of human investigation and ingenuity, the new knowledge is a celebration of human creativity, and the new powers are a reminder of human obligations to act responsibly.

(2) Genetic engineering techniques are advancing very rapidly. Two breakthroughs in animal experiments during 1981 and 1982, for example, bring human applications of gene splicing closer: in one, genetic defects have been corrected in fruit flies; in another, artificially inserted genes have functioned in succeeding generations of mammals.

(3) Genetic engineering techniques are already demonstrating their great potential value for human well-being. The aid that these new developments may provide in the relief of human suffering is an ethical reason for encouraging them.

- Although the initial benefits to human health involve pharmaceutical applications of the techniques, direct diagnostic and therapeutic uses are being tested and some are already in use. Those called upon to review such research with human subjects, such as local Institutional Review Boards, should be assured of access to expert advice on any special risks or uncertainties presented by particular types of genetic engineering.

- Use of the new techniques in genetic screening will magnify the ethical considerations already seen in that field because they will allow a larger number of diseases to be detected before clinical symptoms are manifest and because the ability to identify a much wider range of genetic traits and conditions will greatly enlarge the demand for, and even the objectives of, prenatal diagnosis.

(4) Many human uses of genetic engineering resemble accepted forms of diagnosis and treatment employing other techniques. The novelty of gene splicing ought not to erect any automatic impediment to its use but rather should provoke thoughtful analysis.

- Especially close scrutiny is appropriate for any procedures that would create inheritable genetic changes; such interventions differ from prior medical interventions that have not altered the genes passed on to patients' offspring.
- Interventions aimed at enhancing "normal" people, as opposed to remedying recognized genetic defects, are also problematic, especially since distinguishing "medical treatment" from "nonmedical enhancement" is a very subjective matter; the difficulty of drawing a line suggests the danger of drifting toward attempts to "perfect" human beings once the door of "enhancement" is opened.

(5) Questions about the propriety of gene splicing are sometimes phrased as objections to people "playing God." The Commission is not persuaded that the scientific procedures in question are inherently inappropriate for human use. It does believe, nevertheless, that objections of this sort, which are strongly felt by many people, deserve serious attention and that they serve as a valuable reminder that great powers imply great responsibility. If beneficial rather than catastrophic consequences are to flow from the use of "God-like" powers, an unusual degree of care will be needed with novel applications.

(6) The generally very reassuring results of laboratory safety measures have led to a relaxation of the rules governing gene splicing research that were established when there was widespread concern about the potential risks of the research. The lack of definitive proof of danger or its absence has meant that the outcome—whether to restrict certain research—has turned on which side is assigned the burden of proving its case. Today those regulating gene splicing research operate from the assumption that most such research is safe, when conducted according to normal scientific standards; those opposing that position face the task of proving otherwise.

- The safety issue will arise in a wider context as gene splicing is employed in manufacturing, in agriculture and other activities in the general environment, and in medical treatment. As a matter of prudence, such initial steps should be accompanied by renewed attention to the issue of risk (and by continued research on that subject).
- Efforts to educate the newly exposed population to the appropriate precautions, whenever required, and serious efforts to monitor the new settings (since greater exposure increases the opportunity to detect low-frequency events) should be encouraged. In general, the questions of safety concerning gene splicing should not be viewed any differently than comparable issues presented by other scientific and commercial activities.

(7) The Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health has been the lead Federal agency in genetic engineering. Its guidelines for laboratory research have evolved over the past seven years in response to changes in scientific attitudes and knowledge about the risks of different types of genetic engineering. The time has now come to broaden the area under scrutiny to include issues raised by the intended uses of the technique rather than solely the unintended exposure from laboratory experiments.

- It would also be desirable for this "next generation" RAC to be independent of Federal funding bodies such as NIH, which is the major Federal sponsor of gene splicing research, to avoid any real or perceived conflict of interest.

(8) The process of scrutiny should involve a range of participants with different backgrounds—not only the Congress and Executive Branch agencies but also scientific and academic associations, industrial and commercial groups, ethicists, lawyers, religious and educational leaders, and members of the general public.

- Several formats deserve consideration, including initial reliance on voluntary bodies of mixed public-private membership. Alternatively, the task could be assigned to this Commission's successor, as one among a variety of issues in medicine and research before such a body, or to a commission concerned solely with gene splicing.
- Whatever format is chosen, the group should be broadly based and not dominated by geneticists or other scientists, although it should be able to turn to experts to advise it on the laboratory, agricultural, environmental, industrial, pharmaceutical, and human uses of the technology as well as on international

scientific and legal controls. Means for direct liaison with the government departments and agencies involved in this field will also be needed.

(9) The need for an appropriate oversight body is based upon the profound nature of the implications of gene splicing as applied to human beings, not upon any immediate threat of harm. Just as it is necessary to run risks and to accept change in order to reap the benefits of scientific progress, it is also desirable that society have means of providing its "informed consent," based upon reasonable assurances that risks have been minimized and that changes will occur within an acceptable range.

Clarifying the Issues

1

Human beings continually pursue greater knowledge about themselves and their world. Science provides a powerful key in that quest, unlocking many mysteries. But even as science answers questions, it generates many new ones; new knowledge creates new challenges. The recently acquired capability to manipulate the genetic material of all living things is an important—even revolutionary—advance in the trajectory of human knowledge. But, like revolutionary insights of the past that enriched understanding, it also unsettles notions that once seemed fixed and comfortable. This Report attempts to contribute to the public discussion of the social and ethical implications of genetic engineering by clarifying some of the issues raised by the new technology and initiating an examination of possible procedural mechanisms for responding to them.

The Commission undertook this study in response to a request addressed to the President on June 20, 1980, by the General Secretaries of the National Council of Churches, the Synagogue Council of America, and the United States Catholic Conference. In the wake of the Supreme Court decision that allowed the patenting of new forms of life, the religious organizations warned that

> We are rapidly moving into a new era of fundamental danger triggered by the rapid growth of genetic engineering. Albeit, there may be opportunity for doing good; the very term suggests the danger.[1]

Describing the questions as "moral, ethical, and religious, [dealing] with the fundamental nature of human life and the dignity and worth of the individual human being," the three

[1] For the full text of the letter from the religious bodies, see Appendix B, pp. 95-96 *infra.*

religious representatives called upon President Carter to remedy the lack of "adequate oversight or control" among governmental bodies by providing "a way for representatives of a broad spectrum of our society to consider these matters and advise the government on its necessary role." In response to a request from the President's Science Advisor, the Commission decided in September 1980 to study the ethical and social implications of this new area of biotechnology as it applies to human beings.

The Meaning of the Term "Genetic Engineering"

Changes in the Genetic Landscape. For at least 10,000 years—since long before the principles of classical genetics[2] had been scientifically established—human beings have brought about deliberate genetic changes in plants and animals through traditional reproductive methods. Many of the domestic animals, crops, and ornamental plants in existence today are human creations, achieved through selective breeding aimed at enhancing desired characteristics. In a broad sense, such genetic manipulation by breeding for a desired outcome might be considered genetic "engineering."

In addition to these intended changes, many alterations have occurred inadvertently through other practices, including the ordinary practice of medicine. Many people with genetic disorders who in the past would have died without any natural-born children now live into adulthood, passing on genes for the disorder. The use of exogenous insulin to treat diabetes and the prescription of eyeglasses for myopia are two examples of interventions that increase the prevalence in the population of certain genes that can have deleterious effects for individuals. Medical screening for genetic disorders and carrier status, when followed by decisions by the individuals screened to alter reproductive behavior, also affects the occurrence of genes in the population.[3] These changes have been a by-product of medical and technological interventions aimed at individuals, not at the general population.

Manipulating Genes. In 1965 the term "genetic engineering" was coined for what has come to be a wide range of techniques by which scientists can add genetically determined characteristics to cells that would not otherwise have possessed them.[4] Compared with traditional means of altering the

[2] For definitions of the technical terms used throughout this Report, see *Glossary*, Appendix A, pp. 89-93 *infra*.

[3] A discussion of genetic screening can be found in the Commission's report, SCREENING AND COUNSELING FOR GENETIC CONDITIONS, U.S. Government Printing Office, Washington (1983).

[4] Rollin D. Hotchkiss, *Portents for a Genetic Engineering*, 56 J. HEREDITY 197 (1965).

gene pool, the ability to alter genetic material directly offers specificity and, in the case of changes in germ cells, speed.

The rapidity with which this field has developed is startling. Scientists' understanding of the structure of deoxyribonucleic acid (DNA), which is common to almost all living cells, and their discovery of its remarkable capacity for encoding and passing on genetic characteristics are post-1953 developments. In the early 1970s, scientists learned how to isolate specific DNA sequences from one species and attach this genetic material—"recombinant DNA"—to a different species. Rapid progress has also been made with cell fusion, another means of genetic engineering that permits the contents of two cells from different organisms to be merged in such a way that the hybrid cell continues to function and reproduce.

The layperson's term "gene splicing" describes the technology well, for like a seaman putting two pieces of rope together, a scientist using the recombinant DNA method can chemically "snip" a DNA chain at a predetermined place and attach another piece of DNA at that site. In cell fusion, it is two entire cells that are "spliced" together. Chapter Two provides a fuller discussion of gene splicing and its applications.

The term genetic engineering has sometimes been used to refer to several other new technologies such as *in vitro* fertilization[5] and cloning[6] of an organism. These techniques do

[5] *In vitro* fertilization (IVF) is a technique for achieving fertilization of an egg outside of the body, in a laboratory dish (from the Latin, *in vitro,* for "in glass"). In its therapeutic uses it also encompasses embryo transfer to a uterus. One or more eggs are surgically removed from an ovary of a woman with obstructed Fallopian tubes, fertilized with her husband's sperm in a laboratory dish, allowed to develop there for a few days, and then transferred into the woman's uterus, where the pregnancy proceeds. IVF has received a great deal of publicity in the past few years as some previously infertile women have given birth following the use of this technique. The Commission decided in May 1980 not to take up the subject of human *in vitro* fertilization because the Ethics Advisory Board of the Department of Health and Human Services had studied the subject at length. Action has not yet been taken on the EAB's May 4, 1979, report and recommendations to the Secretary.

[6] Cloning, the production of genetically identical copies, can apply to cells or whole organisms. Although the idea of creating clones in the laboratory is new, many species of plant and animals, including humans, produce natural clones. For example, identical twins, triplets, etc., are members of a clone, since they are derived from the same fertilized egg.

In 1981 researchers produced a clone of mice from embryonic cells. Nuclei taken from a seven-day-old embryo were inserted into newly fertilized mouse eggs from which the nuclei had been removed. Jean L. Marx, *Three Mice "Cloned" in Switzerland,* 211 SCIENCE 375 (1981). These eggs were then implanted into the uterus of "foster

not necessarily involve genetic manipulation, although they might be used in conjunction with such manipulation in particular situations. They are regarded here as examples of reproductive (rather than genetic) technologies and thus are outside the scope of this Report.

Concerns About Genetic Engineering

Genes are perhaps the most tangible correlates of who a person is as an individual and as a member of a family, race, and species. They are people's fixed legacy to their descendants. Genetic information can alter an individual's most personal decisions about reproduction. It is not surprising, therefore, that genetics is peculiarly prone to controversy.

Scientific Self-Regulation. Although issues in genetics arouse wide public interest, the initial concern about genetic engineering did not come from the public but from scientists actually involved in the research. Genetic material is essentially the same in most living things, and therefore in theory gene transfers can be carried out between any two organisms. In the early 1970s fears that exploiting this interchangeability could cause the uncontrollable spread of serious disease or damage the environment led some of the first scientists working with gene splicing techniques to raise questions about the unpredictable consequences of their work. For example, one of the early planned experiments involved attempts to splice SV40, a virus known to cause cancer in mice and hamsters, into a bacterium. What, scientists wondered, would happen if that experimental bacterium was released outside the laboratory and began making billions of copies of itself—and its new cancer-causing gene? The worries were compounded by the fact that the experimental bacterium was closely related to one normally found in human beings. Was it possible that the laboratory bacterium, carrying a cancer virus, might be infectious in humans or cause a cancer epidemic?

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mothers" who subsequently gave birth to genetically identical mice. The success demonstrated that the embryonic cells retain their totipotency [that is, their ability to develop into a complete mouse). Developing a clone from an existing individual, rather than embryonic cells, is more difficult since these cells have already differentiated and would need to regain totipotency.

In light of the public attention cloning has received, it is important to emphasize that even if a cell from a developed organism could produce a clone, it would not result in an instantaneous "carbon copy" of the original. In cloning, the genetic material is inserted into a recently fertilized egg to produce a new generation with the same genetic makeup. The technology to clone a human does not—and may never—exist. Moreover, the critical nongenetic influences on development make it difficult to imagine producing a human clone who would act or appear "identical."

Such concerns led in the fall of 1973 and summer of 1974 to the publication, in both *Science* and *Nature*, of letters signed by several leading molecular biologists on behalf of those most centrally involved in the field.[7] The first letter called attention to the issues and asked the National Academy of Science to establish a committee, and the second urged scientists to hold off on certain recombinant DNA experiments until the risks could be assessed. This process of assessment was pushed forward by the new NAS committee, chaired by Paul Berg of Stanford University, which organized a meeting in February 1975 at the Asilomar conference center in California. At the meeting were 150 molecular biologists, microbiologists, plant physiologists, industrial researchers, and other scientists from both the United States and abroad, four American lawyers, and a large group of journalists as observers. The Asilomar participants proposed that the self-imposed moratorium be lifted for most recombinant DNA research, subject to specified physical and biological containment measures that would be graduated according to the risk of the experiment.[8]

Governmental Supervision. After the meeting, the Director of the National Institutes of Health (NIH) asked the Recombi-

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[7] Maxine Singer and Dieter Soll, *Guidelines for DNA hybrid molecules* (Letter), 181 SCIENCE 1114 (1973); Paul Berg *et al.*, *Potential biohazards of recombinant DNA molecules* (Letter), 185 SCIENCE 303 (1974). Taking as his starting point the recombinant DNA experience, a leading ethicist has argued for an expanded vision of scientific responsibility;

> If the essence of good scientific research is to leave no stone unturned, it is no less pertinent to moral thought. A scientific researcher would, in strictly scientific terms, be considered poor if he did not allow his mind to roam in all directions during the phase of hypothesis development, taking seriously any idea that might produce a promising lead....The same is true of moral thinking, particularly when it bears on the future consequences of our actions. We are obliged to explore all possibilities, however vague and remote; and the moral person will also end by throwing most of them out—most, finally, but not all. Since we surely now know that scientific research, whether basic or applied, is a source of enormous power for both good and ill, the scientific researcher has, then, an obligation to be as active in his moral imagination as in his scientific imagination. We ask the same of any person in a position of power.

Daniel Callahan, *Ethical Responsibility in Science in the Face of Uncertain Consequences*, 265 ANN. N.Y. ACAD. SCI. 1,6 (1976).

[8] Michael Rogers, BIOHAZARD, Alfred A. Knopf, New York (1973) at 51-101; William Bennett and Joel Gurin, *Science that Frightens Scientists*, THE ATLANTIC 43, 49-50 (Feb. 1977); Roger B. Dworkin, *Science, Society, and the Expert Town Meeting: Some Comments on Asilomar*, 51 S. CAL. L. REV. 1471 (1978).

nant DNA Advisory Committee (RAC) that had been established the previous October to consider the Asilomar report and make recommendations. RAC issued guidelines in June 1976 (under the auspices of NIH) for the conduct of recombinant DNA experiments.[9] The guidelines are binding on researchers receiving Federal funds, and—the Commission was informed during this study—the private sector has complied with them voluntarily.

Concern about "biohazards" also found its way to Capitol Hill. Several bills were introduced in the mid-1970s to regulate gene splicing research, although none passed.[10] The political rhetoric of proponents and opponents escalated as the debates moved to the community level; in Cambridge, Massachusetts, and some other localities with major research institutions, concerns about the safety of recombinant DNA experiments aroused loud and often vitriolic public debates.[11] Several communities enacted ordinances restricting gene splicing research.[12]

Meanwhile, RAC became a "second generation" body in which scientific members were joined by a larger representation of public members. As a 25-member body that now meets three to four times a year, it continues to oversee implementation of the NIH guidelines. Those restrictions have been progressively relaxed as scientists have gained experience with the new technology; for most types of experiments, the

[9] 41 Federal Register 27902 (July 7, 1976).

[10] In total, 16 bills related to recombinant DNA research were introduced in the 95th Congress, in addition to numerous proposed bills that were considered but never formally introduced. For a listing of the bills see National Institutes of Health, RECOMBINANT DNA RESEARCH VOLUME 2, DOCUMENTS RELATING TO "NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES" JUNE 1976-NOVEMBER 1977, U.S. Dept. of Health, Education and Welfare, Washington (1978).

[11] Nicholas Wade, THE ULTIMATE EXPERIMENT, Walker and Company, New York (1977) at 127-41.

[12] The Cambridge statute incorporated by reference the RAC guidelines (applying them to industry as well as universities) and established a Cambridge Biohazards Committee for oversight. Between 1977 and 1979 New York and Maryland and five towns, from New Jersey to California, followed the Cambridge model; in 1981 and 1982 a second wave of legislation was enacted in several communities in the Boston area addressed specifically to the commercial uses of recombinant DNA technology. Sheldon Krimsky, *Local Monitoring of Biotechnology: The Second Wave of Recombinant DNA Laws,* 5 RECOMBINANT DNA TECHNICAL BULL. 79 (1982). *See also* Cambridge, Mass. Ordinance 955, Ordinance for the Use of Recombinant DNA Technology in the City of Cambridge (April 2, 1981); Waltham, Mass. General Ordinances ch. 22 (1981); Michael D. Stein, *Boston Strikes Out: Local DNA Guidelines,* 292 NATURE 283 (1981).

opponents now bear the burden of proving danger, rather than the proponents having to prove safety.[13]

No physical injuries have been found to have resulted from new organisms created with gene splicing techniques. Most molecular biologists now say they believe that the original worries were exaggerated. Nevertheless, a few scientists continue to maintain that some questions remain unanswered and that continued caution is desirable. This conservative approach influenced RAC enough that the committee decided in early 1982 not to convert the guidelines into a voluntary code of good laboratory practice. Some RAC members also worried that the Federal withdrawal from the field would lead states and localities to adopt varying, and often more onerous, regulations.[14]

Deeper Anxieties. While the political, public, and scientific debate has focused on the hazards of pathogenic organisms, it has become apparent that the implications of gene splicing are more far-reaching. The consequences of mistakes or failures in the laboratory have received attention, but success in learning how to manipulate genes could have enormous societal consequences as well. The fact that in the mid-1970s laboratory experiments with recombinant DNA were assumed for a time to be quite risky ought not to mean that forever thereafter any research in gene splicing has to overcome a presumption of danger.[15] Nevertheless, new knowledge does carry a responsibility—often weighty—for its application, and the implications

[13] To suggest that the "burden of proof" issue lies at the heart of the recombinant DNA debate is not to suggest that it is a single issue or, indeed, that one determination of *who* bears *what* burden of going forward with *what* evidence and persuading *whom* will be satisfactory for all aspects of public policy regarding recombinant DNA. One ground for suggesting different burdens might be that the risks motivating concern in the first place are of different sorts [*i.e.,* physical versus social risks]. Another way of slicing the conceptual pie is according to the stage of the research process, between the risks of *means*...and the risks of *ends.*

A.M. Capron, *Prologue: Why Recombinant DNA?,* 51 S. CAL. L. REV. 973, 977 (1978).

[14] Marjorie Sun, *Committee Votes to Keep DNA Rules Mandatory,* 215 SCIENCE 949 (1982).

[15] It is generally true that scientific researchers need not demonstrate the safety of their investigations as a condition of proceeding. But can review be triggered by the expression of genuine concern about risks by knowledgeable parties? In the case of recombinant DNA, do the initial warnings by scientists of possible disasters from research mishaps have continuing force once the same scientists suggest that subsequent experience has led them to doubt that any unusual risk exists? In other words, once triggered can a process of decision be called

of genetic engineering for new knowledge and novel applications are wide-ranging.

The public's anxiety over genetic engineering may have focused at first—in the wake of press accounts of the Asilomar conference—on biohazards but deeper concerns soon became apparent. In announcing hearings in Cambridge on Harvard's proposed recombinant DNA laboratory in 1976, Mayor Alfred E. Vellucci gave voice to the general disquiet about genetic engineering: "They may come up with a disease that can't be cured—even a monster. Is this the answer to Dr. Frankenstein's dream?"[16]

This "Frankenstein factor"[17] conveys the public uneasiness about the notion that gene splicing might change the nature of human beings, compounded by the heightened anxiety people often feel about interventions involving high technology that rests in the hands of only a few. Indeed, the frequent repetition of the Frankenstein theme by scientists as well as members of the public is quite apt.

Dr. Frankenstein was a creator of new life; gene splicing has raised questions about humanity assuming a role as creator. As a biologist and an eloquent observer of science notes:

> The recombinant DNA line of research is already upsetting, not because of the dangers now being argued about but because it is disturbing in a fundamental way, to face the fact that the genetic machinery in control of the planet's life can be fooled around with so easily. We do not like the idea that anything so fixed and stable as a species line can be changed. The notion that genes can be taken out of one genome and inserted in another is unnerving.[18]

Some scientists were quite unsettled by the prospect. One leading scientist—who had been an articulate proponent in the 1960s of the hope for improvement that science offered to the "losers" in nature's "genetic lottery"—came to have grave reservations:

> Do we want to assume the basic responsibility for life on this planet—to develop new living forms for our own purposes? Shall we take into our hands our own future

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off by anything short of a judgment on the merits?

Capron, *supra* note 13.

[16] John Kifner, *"Creation of Life" Experiment at Harvard Stirs Heated Dispute,* N.Y. TIMES, June 17, 1976, at A-22.

[17] Willard Gaylin, *The Frankenstein Factor,* 297 NEW ENG. J. MED. 665 (1977).

[18] Lewis Thomas, *The Hazards of Science,* 296 NEW ENG. J. MED. 324, 326 (1977).

> evolution?... Perverse as it may, initially, seem to the scientist, we must face the fact that there can be unwanted knowledge.[19]

Dr. Frankenstein's creation was a frightening monster; gene splicing has raised fears about strange new life forms. Some of these—particularly in the popular press—were far-fetched:

> Simply put, you take a cell from some plant or animal and extract the chemical (DNA) that governs all the physical and mental characteristics of the whole being. Do the same with another, totally different, plant or animal. Graft the two together, Presto! Shake hands with an orange that quacks, with a flower that can eat you for breakfast--or even with the Flying Nun.[20]

Other concerns with new genetic combinations were more immediate. Some biologists pointed to what they believed are the rigid natural barriers against transfer of genetic material between lower life forms that lack a defined nucleus (such as bacteria) and higher forms (such as plants and animals). Particularly in so-called. shotgun experiments, in which the genetic information in an animal cell is broken into many pieces and each is inserted into bacteria so that it will multiply and can be studied, these scientists voiced concern that some of the genetic material might prove very harmful in its new setting even though a risk is not shown, or perhaps does not even exist, when it is part of the total package of genetic material in the original ce11.[21]

The Frankenstein story also seems appropriate because the scientist there sought to control his monster, calling to mind the concerns raised about the distribution of power and control associated with gene splicing: "Each new power won *by* man is a power *over* man as we11."[22] Of equal or greater concern was the view, expressed by some scientists, that even the scientists could not control the "monster." The basic concern about laboratory-generated biohazards lay with a global epidemic from a new pathogen that is resistant to conventional antibiotics or other therapies. As one leading scientist remarked, "You

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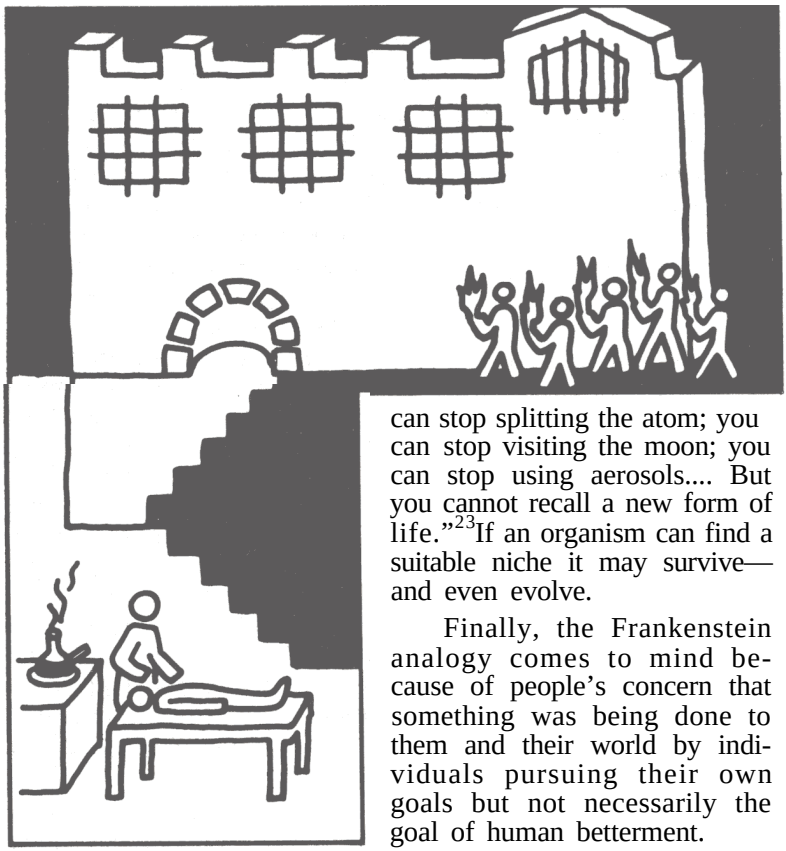
[19] Bernard Dixon, *Tinkering with genes,* 235 SPECTATOR 289 (1975) (quoting Robert L. Sinsheimer, Chairman, Department of Biology, Caltech).

[20] Susan Carson, *New Origin of Species,* WINNIPEG TRIBUNE, July 2, 1979 (CANADIAN Magazine), at 2.

[21] Erwin Chargaff, *On the Dangers of Genetic Meddling* (Letter), 192 SCIENCE 938 (1976).

[22] C. S. Lewis, THE ABOLITION OF MAN, Collier-Macmillan, New York (1965) at 71.



can stop splitting the atom; you can stop visiting the moon; you can stop using aerosols.... But you cannot recall a new form of life."[23] If an organism can find a suitable niche it may survive—and even evolve.

Finally, the Frankenstein analogy comes to mind because of people's concern that something was being done to them and their world by individuals pursuing their own goals but not necessarily the goal of human betterment.

> Working in his dungeon laboratory, Dr. Frankenstein can't be bothered by intruders. He is a genius, he has uncovered the secret of life, and no one can stop his research. Only when his monster begins to destroy does he realize what he has done; and by then it is too late.[24]

Mayor Vellucci of Cambridge voiced what may be a widely held skepticism about researchers when he declared: "I don't think these scientists are thinking about mankind at all. I think that they're getting the thrills and the excitement and the passion to dig in and keep digging to see what the hell they can do."[25] The fear was that for researchers, creating a new life

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[23] Charles A. White, *It's not nice to fool with mother nature*, 43 CANADA & THE WORLD 10, 11 (1977) (quoting Erwin Chargaff, a biochemist at Columbia University). Professor Chargaff also asked "[H]ow about the exchange of genetic material [among microorganisms] in the human gut? How can we be sure what would happen once the little beasts escaped from the laboratory?" Chargaff, *supra* note 21, at 939.

[24] Arthur Lubow, *Playing God with DNA*, 8 NEW TIMES 48, 61 (Jan. 7, 1977).

[25] *Id.*

form—even a monster—would be a matter of curiosity; for the public, it would be an assault on traditional values.

Thus, as the laboratory hazards of gene splicing were being contained, concerns about the hazards this technology could pose to human and social values began to bubble to the surface of public awareness. Some scenarios were far-fetched and some fears exaggerated, but in general the concerns did reflect an awareness that a biological revolution with far-reaching implications was taking place. In the Commission's view, there is good reason to attend to these worries, including those that do not involve the sorts of physical hazards that have received most attention thus far. New ideas can change the world in psychological and philosophical terms just as radically as new techniques can change it materially. Many examples exist of such changes being wrought by the discoveries of science. In the sixteenth century Copernicus showed that the earth revolved around the sun, not the sun around the earth, and thus upset the notion that humanity was at the center of the universe. Similarly, in the last century, the theory of evolution propounded by Charles Darwin challenged the belief that human beings were uniquely created by claiming that they are the biological kin to other living things and that species have slowly differentiated through the undirected agency of natural selection among randomly occurring changes.

The recent work in molecular genetics may again unseat some widely held—if only dimly perceived—views about humanity's place in nature and even about the meaning of being human. Old concepts are already being revised by some scientists, and it cannot be long before the new knowledge and new scientific powers begin to have an impact on general thinking. As a biochemical researcher observed:

> Once we thought the DNA of complex organisms was inscrutable. Now we cope with it readily. We thought of DNA as immovable, a fixed component of cells. Now we know that some modules of DNA are peripatetic; their function depends on their ability to move about....We thought genes were continuous stretches of DNA. Now we know...(they)...may be interrupted dozens of times, and spliced together...when needed. We have learned that genes are fungible; animal genes function perfectly well within bacteria and bacterial genes within animal cells, confirming the unity of nature. We need no longer depend on chance events to generate the mutations essential for unraveling intricate genetic phenomena.[26]

[26] Maxine Singer, *Recombinant DNA Revisited* (Editorial), 209 SCIENCE 1317 (1980).

The Commission's Study

Some of the less tangible issues in gene splicing were reflected in the religious organizations' June 1980 letter to the President, which expressed concern that "no government agency or committee is currently exercising adequate oversight or control, nor addressing the fundamental ethical questions (of genetic engineering) in a major way." At its regular meeting in July 1980, the President's Commission took note of this expression of concern and decided to explore the issues through a hearing in September.

At the September 1980 meeting, the Commission heard testimony from scientists, philosophers, and public administrators about ethical, social, and scientific aspects of the subject. The Commission learned that the government's jurisdiction over aspects of genetic engineering is both extensive and diverse. A Commission survey revealed no fewer than 15 government agencies with some involvement or potential involvement in genetic engineering. This includes the conduct and funding of research related to plants, animals, and human beings; authority to regulate the products of gene splicing (for example, drugs) and its by-products (such as occupational and environmental risks); and a range of other activities, including studies of nonhuman implications of genetic technology and an assessment of the role of the United States in the development of the technology worldwide.[27]

Amidst this diversity, however, the common focus of government agencies has been on concrete or practical concerns involving health, environmental, and commercial consequences of the new technology. In deciding to undertake a study of this subject, the Commission specifically excluded the issue of laboratory "biohazards." This reflected the Commission's conclusion that the latter subject was receiving considerable attention and being addressed in both the public and private sector. Morever, it seemed more appropriate for this Commission to examine the broader social and ethical issues in genetic engineering and their significance for public policy.

Objectives. In exploring those issues, the Commission found that the concerns are heterogeneous to a remarkable degree. Many of them are concrete and practical; others are vague and imprecise. Some are concerns about avoiding undesirable consequences of the technology or achieving its potential benefits, while others reflect uncertainty about whether a particular application of gene splicing is in fact beneficial or undesirable.

[27] For the results of the survey, see Appendix C, pp. 97-106 *infra*.

The Commission also recognizes that some of the concerns are about future issues that might or might not occur. As discussed in Chapter Two, developments in this field have been swift. Nevertheless, predicting precisely how this technology will develop and how many of its potential applications will be realized is impossible. Direct human applications of gene splicing have only recently begun. Significant technical barriers still impede many potential applications of the technology; sometimes even making progress reveals new hurdles.

Although much remains to be learned in this field, knowledge is being acquired rapidly: in most areas of research, "new" means something that has been found within the past five years; in molecular biology, it often means something found within the past few months. Time and time again in the past ten years, the speed with which events have unfolded has taken well-informed observers by surprise, as noted in a major medical journal:

> While physicians won't be performing gene therapy on humans for some time, that time appears to be approaching more rapidly every day. The tempo of applications of new, basic technologies to clinical medicine continues to be astonishing.[28]

Indeed, prognostications thus far have frequently underestimated the pace of new knowledge.

The most predictable aspect of this technology may be its very unpredictability. The Commission shares the view of the religious leaders, scientists, and others in the media, government, and elsewhere: a continuing exploration is needed of the implications of this technology that has already reshaped the direction of scientific research and that could revolutionize many aspects of life in the modern world.

No attempt is made in this Report to resolve the myriad social and ethical issues generated by the ability to manipulate the basic material of living things. The Commission found that in many instances the issues had not been clearly and usefully articulated yet. A goal of this Report, therefore, is to stimulate thoughtful, long-term discussion—not preempt it with conclusions that would, of necessity, be premature. At this stage in the public discussion, the Commission believes there are at least four broad prerequisites to the development of effective public policy[29]: (1) educating the public about genetics and about the historical context of genetic manipulations; (2)

[28] Lawrence D. Grouse, *Restriction Enzymes, Interferon, and the Therapy for Advanced Cancer*, 247 J.A.M.A. 1742 (1982).

[29] The Commission uses the term "public policy" broadly to include not only formal laws and regulations but the many programs and policies of individuals and institutions that society decides are acceptable and not in need of direct collective intervention. Public policy is not limited to situations where the government has taken

clarifying the concerns underlying the simplistic slogans that are frequently used; (3) identifying the issues of concern in ways meaningful to public policy consideration; and (4) evaluating the need for oversight and analyzing the responsibilities and capabilities for it both within and outside government.

Educating the public. The United States is a country with ever-increasing dependence on technological and scientific expertise. Public participation in matters that may have substantial personal import often require a fundamental knowledge of highly specialized fields. Individuals who do not acquire such knowledge may hesitate to participate in the public debate, thinking the subject is too complicated for them and best left to the experts. Alternatively, public discussion can be misguided because people lack understanding of scientific facts and appreciation of the known limits and potentials of a new technology. The issues surrounding genetic engineering face both these problems.

Public policy on genetic engineering will need to draw heavily on the wisdom of "experts" who have earned the public's trust and respect. But an informed public is also an essential element of a democratic decisionmaking process. As emphasized in the Commission's report on screening and counseling for genetic conditions, it is important to include genetics in academic curricula—beginning in early grades.[30] Even with effective formal education on genetics, however, the rapid changes taking place in this field make continuing education essential. This Report seeks to contribute to that process not only by demonstrating the need for enlightened public discussion, but also by providing the reader with some basic background about this new technology.[31] Such a background is important not only for examining significant implications of this technology, but also for distinguishing the issues that merit serious attention from fantastic scenarios that have no scientific basis.

The Commission also finds a second type of information related to gene splicing important for public discussions—an understanding of the context in which this new technology

action; indeed, as the Report notes, the Commission concludes that many issues raised by genetic engineering are not proper subjects of government regulation, which is itself a public policy judgment.

[30] SCREENING AND COUNSELING FOR GENETIC CONDITIONS, *supra* note 3, at third section of Chapter Two.

[31] Chapter Two provides technical descriptions of the recombinant DNA process, describes the "state of the art," and offers some perspective on gene splicing's potential and limitations. This information is intended to provide the necessary scientific groundwork for an understanding of the social and ethical concerns and the public policy considerations.

arises. Gene splicing is a revolutionary scientific technique that recasts past ideas and reshapes future directions. Even so, it does not necessarily follow that all its applications or objectives represent a radical departure from the past. Indeed, the question of whether this application differs in significant ways from previous interventions or capacities served as an important guidepost for much of the Commission's discussion of social and ethical concerns about genetic engineering. For example, do the partnerships emerging between industry and academia in regard to gene splicing differ from past interactions in ways that give rise to new concerns or require unique responses? Would replacing a defective gene with a normal one from another person to correct a blood disorder differ socially and ethically from current investigations in which bone marrow is transplanted from one person to another for the same purpose? The Commission attempts to bring this perspective to its discussion of the issues.

Clarifying concerns expressed in slogans. A complex and seemingly mysterious new technology with untapped potential is a ready target for simplistic slogans that try to capture vague fears. This is very much the case with genetic engineering. In Chapter Three, the Commission examines some of the slogans that have been invoked on both sides of the genetic engineering controversy, and attempts to clarify and analyze the concerns they seem to reflect.

A recent public opinion poll, for example, found that the single area of research in which restraint on scientific inquiry was favored is "creation of new life forms."[32] But what is meant by this term? Is bacteria into which a human insulin gene has been inserted a "new life form" that ought not to be created? Is a new hybrid corn offensive? Or is the fear of a new life form really about partially human hybrids?

Concern is also expressed about gene splicing because it will cause human beings to "control evolution" or lead to "an alteration of the gene pool." But humanity's activities have always affected the gene pool. And why would tinkering with genes mean that evolution has been "controlled"?

[32] John Walsh, *Public Attitude Toward Science Is Yes, but-,* 215 SCIENCE 270 (1982).

On the other hand, arguments in favor of caution and control are sometimes met with claims of "academic freedom." What application does this principle have in discussing physical risk to other people? And how ought the value of the pursuit of knowledge be weighed against other values?

Identifying the public policy issues. The diversity of social and ethical issues implies the need for similarly varied responses. A third objective of this Report, therefore, is to organize these issues in a way that is useful both for general understanding and for the formulation of sound public policy. The Commission has focused on the various types of uncertainties associated with the uses of gene splicing techniques: evaluative or ethical uncertainty; conceptual uncertainty; and occurrence uncertainty.

The first type of uncertainty occurs when no societal consensus exists as to whether certain applications of gene splicing are beneficial or undesirable. Should research be conducted to generate means by which "positive" traits could be introduced into a person genetically—for example, by improving memory? Would this be regarded as a socially and ethically desirable application of the technology? Further uncertainty occurs because the determination of what constitutes a "defect" or "disease" varies over time and between cultures.

Conceptual uncertainty refers to the fundamental change in concepts that this new technology can engender. As noted earlier, the notion that genes, once conceived of as fixed, can now be manipulated and exchanged has been described as "unnerving." The significance of this for people's conception of their role in the universe and even for the meaning of being human underlie an important set of concerns.

Concerns like these have not typically arisen in public policy discussions. A limited number of implications of gene splicing, however, do echo issues raised by other technologies that have prompted generally uncontroversial public policy responses. The premarket testing of new drugs is one example. A consensus exists that certain outcomes would be beneficial, such as the development of safe, effective drugs, and others harmful, such as unsafe, ineffective drugs. The uncertainty involved is whether a particular outcome will occur. Policy can be directed specifically at promoting the desirable outcomes and minimizing the likelihood of harmful effects.

Occurrence uncertainty also applies to some issues that cannot be so readily addressed. As with many new technologies, the full range of scientific effects of gene splicing cannot now be predicted with complete certainty. And those effects will be expressed in a future that cannot be known in advance.

Decisions made about the future of this technology and its applications will need to be made with reference to the varied

types of risks and uncertainties at stake in gene splicing. Chapter Three attempts to organize the issues in ways that will foster the development of effective public policy.

Evaluating the need for oversight. Having set out the types of risks posed by gene splicing, the Commission then considers the need for oversight of these issues. A variety of mechanisms, involving both the government and the private sector, are possible. One common feature unites all those that seem appropriate to the Commisson: they draw on, but are not controlled by, gene splicing experts.

The Process of Study. At its July 1980 meeting, the Commission decided that its initial response to the religious leaders' concerns about government oversight would be to survey governmental agencies about their activities in this field. With the aid of a special consultant, a review of the field was also prepared for the Commissioners.

A portion of the September 1980 meeting was devoted to reports by representatives of the most actively involved Federal agencies. In addition, the scientific prospects for, and ethical implications of, the use of genetic engineering in human beings were discussed by several invited witnesses. The Commission decided at that time to add this study to those mandated, according to its statutory authority to do so.[33] During the following two years, the issue was discussed by the Commission at a number of its meetings.

To assist in preparing this Report, the Commission assembled a diverse panel that included representatives from medicine and biology, philosophy and ethics, law, social policy, and the private industrial sector.[34] These consultants held a series of meetings with Commissioners and staff on the direction of the Commission's work in this area and the issues to be addressed. A preliminary analysis of the issues was prepared for discussion by the Commission in July 1981. This and subsequent drafts were submitted to some members of the panel, and comments were also received from other scientists and expert observers of the developments of genetic engineering.

Several knowledgeable people were invited to discuss the draft Report with the Commissioners at a hearing on July 10, 1982, at which time preliminary approval was given to a portion of the Report, subject to a number of suggested changes and additions. A revised draft was reviewed by the Commission at its November 12, 1982, meeting and approved, subject to several editorial changes.

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[33] 42 U.S.C. § 300v-1(a)(2).

[34] For a list of the panel members, see Appendix D, pp. 107-10 *infra.*

The Dawn of a New Scientific Era

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Many of the questions raised about genetic engineering cannot be explored without some understanding of the technical aspects of contemporary genetics and cell biology. Lack of information—or misinformation—not only provokes unwarranted fears but may even mean that legitimate and important questions remain unasked. Yet most Americans have had little formal training in biology, let alone in the specialized fields, such as micro- and molecular biology, that are involved in genetic engineering. Although a brief synopsis is plainly no substitute for a detailed education, some background may be helpful for nonspecialist readers. This chapter of the Report is intended, then, to explain a few essential concepts, to describe several of the most important techniques of genetic engineering, and to show how rapidly this field is moving toward direct human applications.

Discovering Life's Mysteries

What is remarkable about the science of gene splicing is not that it seems strange to laypeople—for all science is arcane to those who do not specialize in its study—but rather how unfamiliar it would be for the geneticists of even one generation ago. The existence of discrete inherited factors (later called genes) was postulated in 1865 by Gregor Mendel, a Moravian abbot who studied the patterns of inheritance in pea plants; his important work relied, however, on inferences about genes, not knowledge about their structure or functioning. Mendel's work lay forgotten until the beginning of this century, when the techniques of classical genetics were developed and physicians began to apply genetic knowledge in diagnosing conditions and in advising people about the conditions known to follow Mendelian patterns. Fifty years passed before Francis

Crick and James Watson proposed the double helix as the structure for deoxyribonucleic acid (DNA), which is sometimes called the "master molecule of life" since almost all living things—including plants, animals, and bacteria—possess it. And the basic technique of gene splicing—a method for cutting and reuniting DNA—is itself only a decade old.[1]

Equally remarkable is that many new discoveries point to further unanswered—and perhaps even unanticipated—questions. The humbling reality of human ignorance is as relevant for those in industry and government who sponsor and regulate scientific research as it is for those who engage in that research. Any attempt to unravel more of life's mysteries can lead in unexpected directions, with unknown risks and benefits. The choices made about proceeding in one direction rather than another—or whether to proceed at all—are not simply matters of original scientific insight or intuition nor even of taking the "next logical scientific step." They also depend upon the judgment of individual scientists, laboratory directors, and public and private sector sponsors, drawing on analogy and conjecture, educated by experience, and reflecting personal and institutional values.[2]

Cells and Genes. The human body is made up of billions of cells. Each cell has a particular function—cells in the gastrointestinal tract produce enzymes that digest food, bone cells provide structural support, and so forth. In spite of their markedly varied functions, most cells share the same structural organization—they have a nucleus, where the genetic information is stored, and cytoplasm, where the specialized products of the cell are made (see Figure 1).

It has been thought that all cells in an organism normally contain exactly the same genetic information, with the exception of the germ cells (sperm and eggs), which carry only half. This information is located on individual packets called chromosomes, which come in pairs, half derived from each parent. Every species of plant or animal has a characteristic number of chromosomes. Humans usually have 23 pairs, or a total of 46; the germ cells have 23 chromosomes, one from each pair, while the somatic cells (the rest of the cells in the body)

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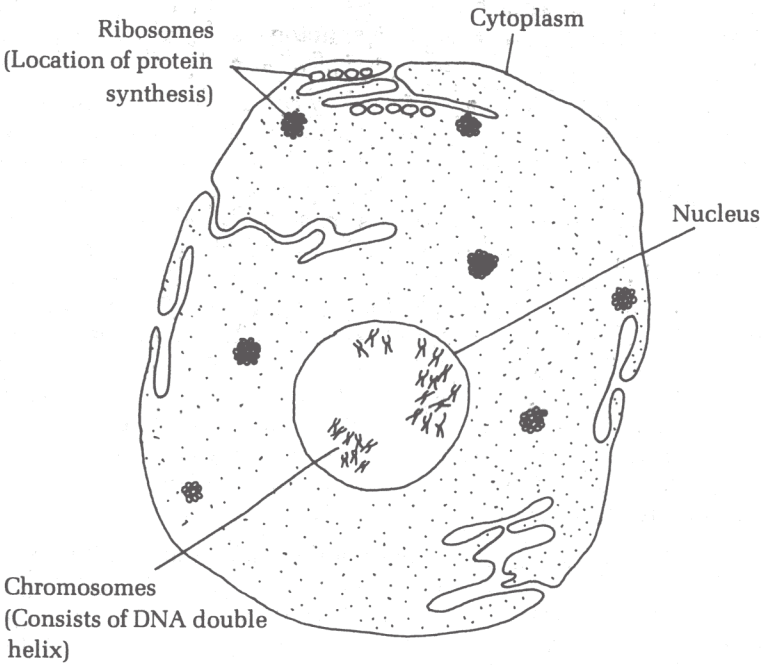
[1] For a history of developments in biochemical and molecular genetics, see Horace Freeland Judson, THE EIGHTH DAY OF CREATION, Simon and Schuster, New York (1979).

[2] Thus, the underlying issue in the recombinant DNA research debate is the accommodation of knowledge-thrust and the public interest. Shall unfolding knowledge determine our desired future or shall our hoped-for future contribute to choices regarding the direction of knowledge-thrust?

Clifford Grobstein, *Regulation and Basic Research: Implications of Recombinant DNA*, 51 S. CAL. L. REV. 1181, 1199 (1978).

Figure 1: Cell Structure



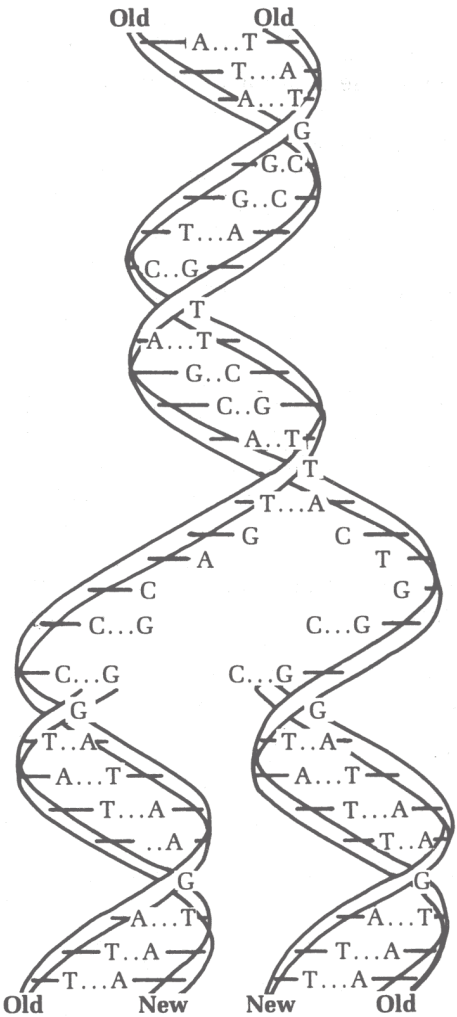
contain a full set of chromosomes. Recent studies have shown that the genetic information is rearranged in some cells; thus far, these findings are limited to the antibody-producing cells.[3]

Each chromosome includes a long thread of DNA, wrapped up in proteins. DNA is made up of chemicals called nucleotides, consisting of one small sugar molecule, one phosphate group, and one of four nitrogenous bases, which can be thought of as the four letters in the genetic alphabet *(A, G, T,* and *C*).[4] DNA consists of two strings of nucleotides lined up

[3] Lymphocytes, the cells that produce antibodies (proteins that protect vertebrates from harm by foreign invaders such as viruses and bacteria), engage in a form of natural recombination whereby the DNA segments needed to construct antibody genes combine in many different ways. Therefore, each clone of lymphocyte cells, which protects against a different invader, has a somewhat different configuration of genes than the other cells in the organism. *See* Maxine Singer, *The Genetic Program of Complex Organisms,* in 3 THE OUTLOOK FOR SCIENCE AND TECHNOLOGY: THE NEXT FIVE YEARS, National Academy Press, Washington (1982) at 1, 24-25.

[4] The four letters are from the name of the base in the nucleotide: A for adenine, G for guanine, T for thymine, and C for cytosine.

Figure 2: Replication of DNA



When DNA replicates, the original strands unwind and serve as templates for the building of new complementary strands. The daughter molecules are exact copies of the parent, with each having one of the parent strands.

Source: Office of Technology Assessment.

next to each other like two sides of a zipper—the phosphates and sugars forming the ribbons and the nitrogenous bases acting like the interlocking teeth. The two strands are twisted around each other in a spiral fashion, forming what Crick and Watson in 1953 labeled a double helix. Each nucleotide is matched with another, to form a pair. That is, the two sides of the zipper can fit together in only one way: *A* paired with *T,* and *G* with *C.*

When a cell divides into two daughter (or progeny) cells—a process called replication—a complete and faithful copy of the genetic code stored on each chromosome is usually transmitted to each daughter cell. Each half of the zipper acts like a template for the creation of its zipper-mate by drawing to itself free nucleotides, which then line up according to the *A-T* and G-C pattern (see Figure 2).

Not all the DNA in chromosomes seems to have a function. The portions with the coded instructions to the cell to perform a particular function (usually to manufacture one particular protein) are called genes. Within the gene are the actual coding regions (called exons), between which are DNA sequences called introns. Genetic information is transferred from the DNA in the nucleus to the cytoplasm by RNA (ribonucleic acid), which is a copy of one strand of the DNA. During this transfer, the introns are spliced out of the RNA. The resulting RNA messengers pass through the cell's protein-synthesizing machinery (called ribosomes), like a punched tape running through a computer to direct a machine's operation.

Proteins—the hormones, enzymes, connecting material, and so forth that give cells and organisms their characteristics—are made up of amino acids. The information carried by the RNA determines how the amino acids combine to make specific proteins. There are 20 amino acids, each one determined by a specific combination of three of the nucleotide "letters" into a "codon." On average, each gene contains slighty more than 300 codons.

Although all cells in an organism carry basically the same genetic material in their nuclei, the specialized nature of each cell derives from the fact that only a small portion of this genetic material (about 5-10%) is active in any cell. In the process of developing from a fertilized egg, each type of cell switches on certain genes and switches off all the others. When "liver genes" are active, for example, a cell behaves as a liver cell because the genes are directing the cytoplasm to make the products that allow the cell to perform a liver's functions, which would not be possible unless all the genes irrelevant to a liver cell, such as "muscle genes," were turned off.

Accidents and Diseases. Occasionally—perhaps because of an error that occurs for some unexplained reason when the cell replicates or because of an outside influence such as a virus or radiation—the specific sequence in a DNA molecule is altered by a change of one or more nucleotides. Such a change is called a mutation. If a mutation occurs in a gene that is active in that cell, the cell will produce a variant protein, as will its daughter cells since they will inherit the same mutation. If other cells of the same type continue to perform their functions properly, the existence of a small amount of variant protein will usually have no adverse effects on the individual.

Some mutations, however, are very harmful; for example, a defective protein can be lethal, or a malignant tumor can result from a mutation that alters a gene in a single somatic cell.

Mutations that occur in somatic cells only affect the progeny of that mutant cell, so that the effects of such mutations are restricted to the individual in whom they occur. In the germ cells, however, mutations result in the altered DNA being transmitted to all cells—somatic and germinal—of an offspring. Inherited mutations that result in deleterious effects are termed genetic diseases. Even though an inherited mutation is present in the DNA sequence of all the body cells, it only affects the function of those specialized cells that manufacture the defective product. For example, a mutation in the gene for rhodopsin (a protein necessary for vision) may result in color blindness, but since the gene is only active in cells in the eye it has no other known effects on a color-blind individual.

The Technology of Gene Splicing

Gene splicing techniques have been understood by scientists for only a decade. During that time, they have been used primarily in microorganisms. Though experiments with higher animals indicated the possibility of using gene splicing for human therapy and diagnosis, numerous hurdles had to be crossed before such steps could be taken. Recent research has cleared some of those hurdles, and work is under way that may conquer the rest much sooner than was thought possible even two years ago, when the Commission began this study.

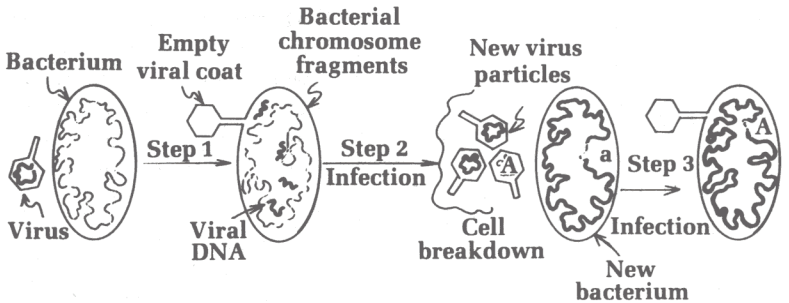
Recombinant DNA Techniques. It was once thought that genetic material was very fixed in its location. Recent findings demonstrate that genetic recombination (the breaking and relinking of different pieces of DNA) is more common between and within organisms—from viruses and bacteria to human beings—than scientists realized. In fact, genetic exchange is a mechanism that may, in evolutionary terms, account for the appearance of marked variations among individuals in a given species.[5]

If DNA replication were the only mechanism for the transfer of genetic information, except for rare instances of mutation each bacterium would always produce an exact copy. In fact, three general mechanisms of genetic exchange occur commonly in bacteria.[6] The first, termed transduction, occurs when the genetic material of a bacteriophage (a virus that

[5] Raoul E. Benveniste and George J. Todaro, *Gene Transfer Between Eukaryotes*, 217 SCIENCE 1202 (1982).

[6] In higher organisms that reproduce sexually, a high degree of genetic variation is produced by the normal process of crossing-over of genes in the germ cells. Crossing-over, like the other processes, involves the formation of new combinations of genes.

Figure 3: Transduction: The Transfer of Genetic Material in Bacteria by Means of Viruses



In step 1 of viral transduction, the infecting virus injects its DNA into the cell. In step 2 when the new viral particles are formed, some of the bacterial chromosomal fragments, such as gene A, may be accidently incorporated into these progeny viruses instead of the viral DNA. In step 3 when these particles infect a new cell, the genetic elements incorporated from the first bacterium can recombine with homologous segments in the second, thus exchanging gene A for gene a.

Source: Office of Technology Assessment.

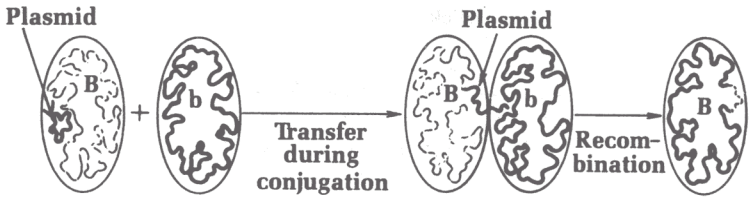
infects bacteria) enters a bacterium and replicates; during this process some of the host cell's DNA may be incorporated into the virus, which carries this DNA along when it infects the next bacterium, into whose DNA the new material is sometimes then incorporated (see Figure 3).

In a second process, called conjugation, bacterial DNA is transferred directly from one microorganism to another. Some bacteria possess plasmids, small loops of DNA separate from their own chromosome, that give the bacteria the ability to inject some of their DNA directly into another bacterium (see Figure 4). And third, bacterial cells can also pick up bits of DNA from the surrounding environment; this is called transformation.

These mechanisms—naturally occurring forms of gene splicing—permit the exchange of genetic material among bacteria, which can have marked effects on the bacteria's survival. The rapid spreading of resistance to antibiotics, such as the penicillin-resistance in gonorrhea bacteria and in *Hemophilus influenzae* (the most frequent cause of children's bacterial meningitis), documents the occurrence of genetic transfers as well as their benefit, from a bacterial standpoint.

The basic processes underlying genetic engineering are thus "natural" and not revolutionary. Indeed, it was the discovery that these processes were occurring that suggested to scientists the great possibilities and basic methods of gene

Figure 4: Conjugation: The Transfer of Genetic Material in Bacteria by Mating



In conjugation, a plasmid inhabiting a bacterium can transfer the bacterial chromosome to a second cell where homologous segments of DNA can recombine, thus exchanging gene B from the first bacterium for gene b from the second.

Source: Office of Technology Assessment.

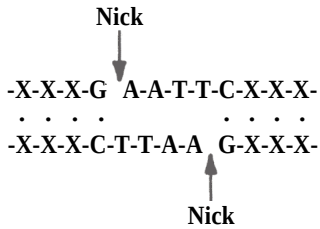
splicing. What is new, however, is the ability of scientists to control the processes. Before the advent of this new technology, genetic exchanges were more or less random and occurred usually within the same species; now it is possible to hook together DNA from different species in a fashion designed by human beings.

The key to human manipulation of DNA came with the discovery, in the early 1970s of restriction enzymes.[7] Each restriction enzyme, of which about 150 have so far been identified, makes it is possible to cut DNA at the point where a particular nucleotide sequence occurs. The breaks, which are termed "nicks," occur in a staggered fashion on the two DNA strands rather than directly opposite each other. Once cut in this fashion, a DNA strand has "sticky ends"; the exposed ends are ready to "stick" to another fragment that has been cut by the same restriction enzyme (see Figure 5). Once the pieces are "annealed" and any remaining gaps are ligated, the "recombinant DNA" strand will be reproduced when the DNA replicates.

Recombinant DNA studies have been performed primarily in laboratory strains of the bacterium *Escherichia coli*, which is normally present in the human intestine. This bacterium possesses only one small chromosome, but it may also contain several ring-shaped plasmids. Plasmids turn out to be useful vehicles (or vectors) by which a foreign gene can be introduced

[7] These enzymes, which make it possible to cut DNA at predetermined places, exist as part of the defense system that bacteria use to respond to foreign DNA (from a virus, for example). Restriction enzymes cut the DNA of the invader into small pieces, while another substance protects the bacteria's own DNA from getting sliced.

Figure 5: Creation of "Sticky Ends" by a Restriction Enzyme

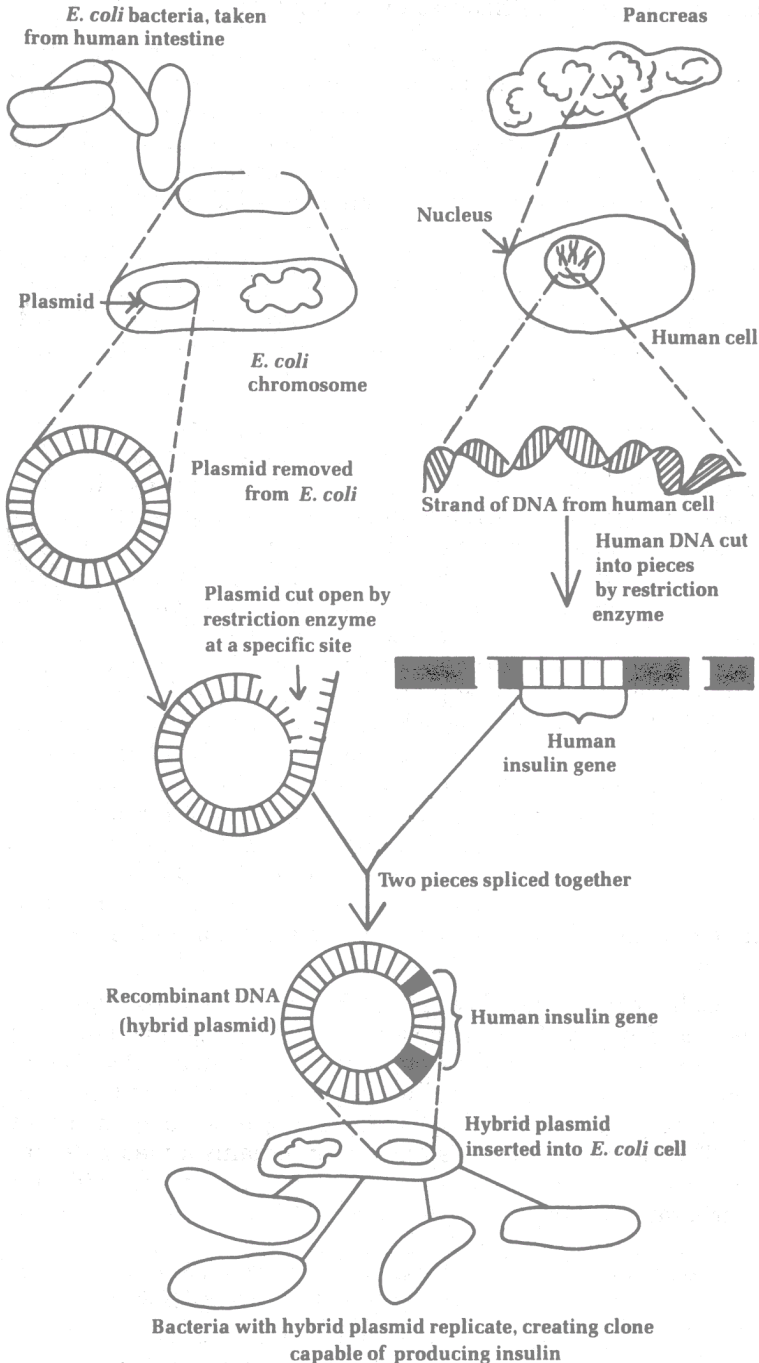


One restriction enzyme produced by E. coli, named Eco RI, recognizes the DNA sequence -G-A-A-T-T-C- on one strand and -C-T-T-A-A-G- on the other. It does not cut clearly across the two strands, however, but between the G and A on both strands, leaving each with exposed bases that can stick to another DNA strand that has been cut in the same fashion and also has an exposed -A-A-T-T sequence.

into the bacterium. A plasmid can be broken open with restriction enzymes, and DNA from another organism (for example, the gene for human insulin) can then be spliced into the plasmid (see Figure 6). After being resealed into a circle, the hybrid plasmid can then be transferred back into the bacterium, which will carry out the instructions of the inserted DNA (in this case, to produce human insulin) as if it were the cell's own DNA. In addition, since plasmids contain genes for their own replication independent of bacterial DNA replication, many copies of the hybrid plasmid will be present in each *E. coli* cell. The end result is a culture of *E. coli* containing many copies of the original insulin gene and capable of producing large amounts of insulin.

The process of isolating or selecting for a particular gene is commonly called cloning a gene. A clone is a group all of whose members are identical. Theoretically, this technology allows any gene from any species to be cloned, but at least two major steps must be taken to make use of this technology. First, it is quite easy to break apart the DNA of higher organisms and insert fragments randomly into plasmids—a so-called shotgun experiment—but identifying the genes on these randomly cloned pieces or selecting only those recombinant molecules containing a specific gene is much more difficult. Because scientists do not yet fully understand what controls gene regulation, inducing expression of the inserted genes has been a second major hurdle. Recently, scientists have been successful in getting a recombinant gene to function in multicell animals and, with the discovery of what are termed transposa-

Figure 6: Splicing Human Gene into Plasmid



Source: President's Commission.

ble elements, even in correcting a defect in some fruit flies' genes.[8] This development serves as a reminder that many technical barriers that loom large are rapidly overcome. Of course, new knowledge sometimes also reveals further, unanticipated technical difficulties to be overcome.

Cell Fusion. Cutting apart DNA chains is not the only way that scientists can transfer genetic material from one cell to another. Cell fusion, which involves the breaking down of cell membranes and the merging of two different types of cells, can also be regarded as a form of genetic engineering although it does not involve direct manipulation of DNA segments. It is being vigorously explored by biomedical scientists who are attempting to map the specific location of human genes on chromosomes and to learn about cellular development and differentiation. These advances should ultimately lead to better understanding, diagnosis, and treatment of various diseases and cancers.

For example, researchers can now produce what are termed monoclonal antibodies. Antibodies are substances produced by the body to fight foreign substances, such as microbial "invaders." Unlike other methods of production, cell fusion techniques have provided especially pure antibodies against a particular invader (or "antigen"). They are called monoclonal because they are produced by a clone of cells descended from a single fabricated original. First, scientists stimulate a mouse to produce antibodies by injecting it with a protein. White blood cells containing an antibody aimed at fighting the "disease" (which is how the mouse's immune system regards the injected proteins) are then fused chemically with malignant cells through a process that involves dissolving and regenerating the cells' outer membranes. This combination—called a hybridoma—inherits the cancer cells' ability to proliferate rapidly and indefinitely and the blood cells' capacity to produce the antibody. Scientists can thus generate a huge clone of cells, which can provide a large amount of the desired antibody.

Cell fusion is not limited to the creation of hybridomas. The 1980 Supreme Court decision that sanctioned the patenting of "new life forms" did not involve recombinant DNA techniques but rather the insertion into bacteria of four naturally occurring plasmids capable of degrading four components of oil.[9] The Court held the resulting microorganism was patentable because it was new (as bacteria in nature did not incorporate all four of the plasmids at once) and useful (as the

[8] Gerald M. Rubin and Allan C. Spradling, *Genetic Transformation of Drosophilia Germ Line Chromosomes*, 218 SCIENCE 348 (1982).
[9] Diamond v. Chakrabarty, 447 U.S. 303 (1980).

genetically engineered bacteria could break down oil spills more rapidly and efficiently).

Genetically Engineered Medical Products

The ability to "engineer" new capabilities into microorganisms has now been used to develop therapeutic and diagnostic agents for human use. This is the first, and thus far the major, use of gene splicing in the medical sphere.

Production of Drugs and Biologics. Most living cells are protein factories, "manufacturing" products according to the "code" of those genes in the cells that are active. Through the use of gene splicing techniques, bacterial cells can be altered so that they will turn out the product encoded by a foreign gene that has been spliced into a plasmid in the bacteria. When such bacteria are then grown in large-scale fermentation broths, huge quantities of valuable medical products are expected to be harvested because bacteria multiply very rapidly—a single bacterium can produce more than a billion copies of itself in 15 hours.

The list of medically useful products that may be obtained through gene splicing techniques is long; a few applications will serve to illustrate. The new technology has already led to the production of several useful human hormones, including human growth hormone to treat dwarfism. To date, many desirable medical products had to be isolated and purified biochemically from natural sources. For example, the insulin consumed by diabetics in this country is isolated from the pancreata of over 80 million cows and pigs each year. Since the supply of pancreas glands is dependent on the demand for beef and pork, gene splicing offers a more stable supply of this essential hormone. Insulin produced with recombinant DNA methods has recently been approved for sale in Great Britain and the United States.[10]

It is predicted that gene cloning of many human hormones will soon be accomplished. Other useful products made by the human body in small quantities are being worked on. For example, there is interest in producing urokinase, which dissolves blood clots and may be useful for treating thrombophlebitis, and anti-hemophilic factor, which is required for blood clotting and is needed to treat hemophilia.

Interferon is another natural product that has attracted much interest for its apparent ability, discovered in 1957, to prevent a virus from proliferating after it invades a body. By the mid-1970s. laboratory evidence suggested that interferon might curtail the spread of certain cancers. Clinical tests and

[10] Lawrence K. Altman, *U.S. Unit Backs Human Insulin for the Market,* N.Y. TIMES, Oct. 30, 1982, at A-1.

therapeutic application proceeded slowly, however, because supplies of interferon were very limited and extremely costly. Most interferon was extracted from cells of donor blood samples in minute quantities, usually laced with impurities. The cost of treating one cancer patient is between $20,000 and $30,000. Therefore, great enthusiasm greeted the prospect of using recombinant DNA techniques to create interferon (a process that also revealed that interferon is not a single substance but a family of related ones, each of which may be effective against certain problems).[11]

Interferon produced through gene splicing is now being tested in clinical trials. Although research to date on interferon obtained by the traditional methods suggests that its potential as the proclaimed "wonder drug" was greatly overstated, the use of gene splicing to produce pure samples in larger quantities offers an opportunity to clarify the many questions that have arisen in the limited existing clinical tests and to resolve some of the issues regarding the use of human interferon in cancer treatment.

Another area of widespread applicability is in the production of useful vaccines. Presently, a weakened strain of a virus must be grown in tissue culture, a tedious chore, before people can be inoculated. There is always a risk that the virus used for inoculation may change into a more virulent strain and actually produce the disease it was meant to protect against. Genetic engineering would allow large-scale production of pure viral components (that is, the protein "coat" of a virus, which is how the body recognizes the virus as a foreign invader and sends out its antibodies to attack it). Such components, being only part of the virus, should be much safer while still conferring immunity. Within the past several years, researchers at MIT reported the cloning of the gene for the protein coat of polio virus and an international team announced it had used recombinant DNA technology to produce the surface antigen associated with the hepatitis B virus.[12] Researchers are also exploring the development of vaccines for certain cancers associated with particular viruses, such as the Epstein-Barr virus and hepatitis B virus, using the antigenicity of the outer coat of the viruses.[13]

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[11] Marjorie Sun, *Interferon: No Magic Bullet Against Cancer,* 212 SCIENCE 141 (1981); Michael Edelhart, *Putting Interferon to the Test,* N.Y. TIMES, April 26, 1981 (Magazine), at 30.

[12] V. R. Racaniello and D. Baltimore, *Cloned Poliovirus Complementary DNA is Infectious in Mammalian Cells,* 20 SCIENCE 916 (1981); P. Charnay *et al., Biosynthesis of Hepatitis B. Virus Surface Antigen in Escherichia Coli.,* 286 NATURE 893 (1980).

[13] Baruch S. Blumberg *et al., The Relation of Infection With the Hepatitis B Agent to Primary Hepatic Carcinoma,* 81 AM. J. PATHOLOGY 669 (1975); Mark Pasek *et al., Hepatitis B Virus Genes and Their Expression in E-Coli,* 282 NATURE 575 (1979). The production of

Cancer Diagnosis and Therapy. A major line of research in oncology today employs genetic engineering technology—in the form of cell fusion—to harness the potential power of monoclonal antibodies in the fight against cancer. Because the human body synthesizes such a huge variety of antibodies, the hope is that antibodies can be produced that are highly targeted for particular tumors and especially for the few cells that remain when a tumor is surgically excised or irradiated. Antibodies tagged with markers (such as trace amounts of radioactive chemicals) can also act like probes, permitting better diagnosis of the location and size of cancers.

Thus far, physicians have reported on only a few dozen cancer patients treated with monoclonal antibodies. The notable results of one of these early trials were announced in March 1982: a man with a rare malignancy that had defied previous treatment received a specially designed antibody and within weeks showed dramatic improvement, including the disappearance or diminution of the tumors that had proliferated throughout his body.[14] Although proof of effectiveness and an understanding of side effects must await years of clinical testing, the theory behind the technique is attractive: target a particular cell for attack by an antibody, or by a chemical poison attached to the antibody, rather than rely on current methods that involve radiation and chemicals that can have devastating effects on the body's normal cells while they attempt to destroy all the cancer cells.

Genetic engineering is also being used by biomedical scientists who are trying to understand and control the recently identified "oncogenes" that apparently direct the wild proliferation of cells that creates a tumor. Sometimes the genetic error involved appears to be inherited; other times it apparently results from damage during a person's lifetime from chemicals, radiation, or a virus. Gene splicing may permit the genetic error to be identified early and even to be treated, although such procedures are not imminent.

Genetic Screening and Diagnosis

One spin-off of recombinant DNA technology exploits the specificity of restriction enzymes to help diagnose the exis-

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vaccines for diseases affecting domestic animals is also being very actively pursued. Other agricultural uses (engineering new traits in plants and animals rather than breeding for these traits), as well as industrial and mining uses of gene splicing, are being vigorously explored in academic and commercial laboratories in this country and elsewhere. Office of Technology Assessment, U.S. Congress, IMPACTS OF APPLIED GENETICS—MICRO-ORGANISMS, PLANTS, AND ANIMALS, U.S. Government Printing Office, Washington (1981).

[14] Richard A. Miller *et al., Treatment of B-Cell Lymphoma with Monoclonal Anti-Idiotype Antibody,* 306 NEW ENG. J. MED. 517 (1982).

tence of or the carrier status for a wide range of genetic disorders that until now have not been readily diagnosable.[15] The technique holds particular promise for prenatal tests and for diagnosis of late-onset disorders such as Huntington's disease. Recombinant DNA techniques allow the DNA of a gene itself to be assessed, unlike previous techniques that necessitate waiting for the gene's product (that is, an identified protein) to be manufactured.

"Restriction enzyme sites" are the specific sequences in the DNA at which one of the 150 known restriction enzymes recognizes and cuts the DNA molecule. Restriction enzymes can provide the basis for a useful assay for a particular gene in two ways: (1) if the molecular variation in the DNA of the gene is known and coincides with the cutting site for a particular restriction enzyme on the gene in question, or (2) if the restriction enzyme site lies on a variant DNA "marker" gene adjacent to the gene of interest, with which it is linked. Both techniques are based upon the fact that specific restriction enzymes cut the DNA into fragments of a characteristic length. If the sequence of the nucleotides is "abnormal" at a point that a restriction enzyme would cut, the enzyme will not cut there but at the next enzyme site, thereby producing a DNA fragment of unusual length.[16]

Mutations in the nucleotide sequence can have harmful, neutral, or beneficial consequences. Those that are deleterious put an organism at a disadvantage for survival and reproduction; hence they usually appear at very low frequencies in a population. On the other hand, some mutations persist with some frequency in a species. Occasionally, these variant forms of DNA—which are called polymorphisms—occur in the portions of the genes that actually code for proteins, apparently because they provide the organism with some survival advantage. Polymorphisms are more frequent in the introns or in the "spacer DNA" (those segments of the chromosomes that lie between the genes) because they do not code for proteins and their precise DNA sequences are thus not crucial for normal functioning.

Some genes that code for variant hemoglobins are relatively frequent, such as the gene that causes sickle-cell disease. It is an example of a mutation that, in the heterozygous form, provides a selective advantage. In regions where malaria was prevalent, people who had one gene for sickle hemoglobin (and

[15] *See, e.g.*, Alan E. Emery, *Recombinant DNA Technology*, 2 LANCET 1406 (1981).

[16] Arlene Wyman and R.L. White, *Restriction Fragment Length Polymorphism in Human DNA*, 77 PROC. NAT'L. ACAD. SCI. 6754 (1980); D. Botstein *et al.*, *Construction of a Genetic Linkage Map in Man Using Restriction Fragment Length Polymorphisms*, 32 AM. J. HUMAN GENETICS 314 (1980).

one for normal hemoglobin) were less likely to die from malaria. In 1978, geneticists' understanding of the mutational site of the sickle-cell variant led to a direct demonstration of the primary gene mutation responsible for sickle-cell disease by using a restriction enzyme that cuts DNA at that site.[17] This procedure allowed the detection of the sickle mutation by an examination of the length of the fragments produced. Thus, sickle-cell anemia—which previously could be diagnosed prenatally only by obtaining a sample of fetal blood (a process that is more difficult and riskier than ordinary amniocentesis)—is diagnosable in fetal cells using recombinant DNA technology, although the procedure is not yet in wide clinical use.

At least in the foreseeable future, scientists do not believe that most genetic diseases will be diagnosable by finding a direct correspondence between a known mutation in the gene and a restriction site since the nature of the DNA mutation in most genetic diseases remains unknown. But two new alternative diagnostic means are now being used for a growing list of genetic conditions. The first, which depends on restriction fragment length polymorphisms, can be used even when the genetic mutation is not known. By using restriction enzymes to reveal variations in spacer DNA and in introns, scientists within a few years will have created a map of genetic landmarks on all chromosomes so that studies of genetic diseases can be undertaken to locate the genes that cause these diseases.[18] Thus, one or another DNA variant will be linked with each genetic disease. When such a "linkage" between an abnormal gene and a DNA polymorphism is used, the closer the restriction enzyme cutting site is to the gene, the more likely it is that they will be inherited together.

To apply this technique to screening, it is necessary to do studies of the genes in a family and develop the linkage patterns between the "marker" DNA and the gene of clinical interest. The finding of a specific DNA pattern in an offspring is only significant for diagnostic purposes when a parent or sibling who has the genetic condition in question has also been typed for the linked marker. Often both parents, and sometimes other relatives, have to be studied to interpret the meaning of the DNA pattern in the child.

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[17] Y.W. Kan and A. M. Dozy, *Antenatal Diagnosis of Sickle-Cell Anemia by DNA Analysis of Amniotic-Fluid Cells,* 2 LANCET 910 (1978).

[18] David T. Bishop *et al., The Number of Polymorphic DNA Clones Required to Map the Human Genome,* in Bruce Weir, ed., STATISTICAL ANALYSIS OF DNA SEQUENCE DATA (in press); Mark H. Skolnick and U. Francke, *Report of the Committee on Human Gene Mapping by Recombinant DNA Techniques,* 32 CYTOGENETICS & CELL GENETICS 194 (1982).

A second new method, termed oligonucleotide hybridization, can be used when the mutation in the gene is known but does not coincide with a restriction enzyme site.[19] An assay can be performed with relatively short synthetic DNA probes that will show whether the gene or the mutant is present. The initial research has been done in a pulmonary disorder, but the first general applications are likely to be in the prenatal diagnosis of the various beta-thalassemias.

Although the diagnostic uses of gene splicing have engendered less controversy than the therapeutic uses (and, hence, receive less attention in this Report), this area of health care is one that recombinant DNA technology is likely to affect most in the immediate future. In effect, these developments will magnify the ethical considerations addressed in the Commission's report on genetic screening and counseling.[20] Genetic engineering techniques will permit the identification of a much wider range of genetic traits and conditions *in utero;* thus, they may greatly broaden the demand for, and even the objective of, prenatal diagnosis.

Difficult social and ethical issues will also be posed by the greatly enhanced ability of genetic screening to identify people with a susceptibility to diseases, some of which are treatable (such as colon cancer in patients with hereditary polyposis, or hemochromatosis, a disease involving a buildup of iron in the blood) and some of which are not (such as Huntington's disease). Genetic screening will probably be much more widely used not only in personal medical care and counseling but also in public health programs, insurance exams, and occupational or pre-employment settings as more is learned about the association between particular genotypes and disease susceptibility. Screening may permit individuals to obtain preventive medical care early or to identify those environments and behaviors that they ought to be especially careful to avoid.[21]

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[19] Savio Woo *et al., Alpha-1 Antitrypsin Deficiency and Pulmonary Emphysema: Identification of Recessive Homozygote by Direct Analysis of the Mutation Site in the Chromosomal Genes,* Cold Spring Harbor Symposium on the Application of Recombinant DNA to Human Disease, 1982 (in press).

[20] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, SCREENING AND COUNSELING FOR GENETIC CONDITIONS, U. S. Government Printing Office, Washington (1983).

[21] Eventually, medical scientists may be able to identify not only restriction enzyme sites that are tightly linked to known gene defects and some that are actually located at the exact site of a mutation, but also the presence or absence of genes that are responsible for other human characteristics, even those that would not be detectable through looking for their biochemical "footprints," as is now done, for example, in measuring the level of serum phenylalanine in screening for phenylketonuria (PKU). Of course, most interesting human charac-

Curing Genetic Disorders

In the immediate future, the most important applications of gene splicing techniques for human health will probably be in the creation of products—hormones, enzymes, vaccines, and so forth—for human consumption and in the development of genetic screening. But in the long run, direct use of the technique in humans can be expected to have an impact that is much more significant in terms of changing people's health and developmental status, and more novel and far-reaching in conceptual and psychological terms. During 1982, the prospect of direct application of gene splicing to cure human genetic diseases moved forward by large steps, although formidable hurdles remain.

The simplest form of human gene splicing would be directed at single gene mutations, which are now known to cause more than 2000 human disorders.[22] Such a defect in just one gene—although each human cell has as many as 100,000 genes—can have tragic and even fatal consequences. Existing treatments of genetic diseases are all palliative rather than curative—that is, they are merely aimed at modifying the consequences of a defective gene. In contrast, gene splicing technology offers the possibility of correcting the defects themselves and thus curing at least some of these diseases. The effects of gene splicing might be limited to the somatic cells of the individual being treated or might, intentionally or otherwise, alter the germ cells, thereby creating a change in the genes that would be passed on to future generations.

Somatic Cells. The basic method proposed for using gene splicing on human beings is termed "gene therapy." This is defined as the introduction of a normal functioning gene into a cell in which its defective counterpart is active. If the mutant gene is not removed but merely supplemented, the cells may continue to produce the defective product alongside the normal product generated by the newly added gene.

Even further in the future is a theoretical possibility, sometimes referred to as "gene surgery," in which not only would the normal gene be added but the defective gene itself would either be excised or its function suppressed, so that it would no longer send out a message for a defective product in competition with the message from the inserted "normal" gene.

The technology, which researchers are now attempting to develop, involves four steps: cloning the normal gene, introducing the cloned genes in a stable fashion into appropriate target

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teristics are believed to result from the interaction of the environment with a number of genes, rather than a single gene, which would make "screening" an exceedingly complex task.

[22] Victor A. McKusick, MENDELIAN INHERITANCE IN MAN, Johns Hopkins Univ. Press, Baltimore (6th ed. 1982).

cells by means of a vector, regulating the production of the gene product, and ensuring that no harm occurs to the host cells in the patient. Only the first step—cloning a normal counterpart of a defective gene—is a straightforward matter with current knowledge and technology.

Introducing copies of the normal gene specifically to a particular set of target cells can, in theory, be achieved. Gene therapy offers the greatest promise for those single-gene defects in which an identifiable product is expressed in a discrete subpopulation of cells. For example, sickle-cell anemia and beta-thalassemia (also called Cooley's anemia) both involve alterations in the hemoglobin gene that is expressed in an accessible subpopulation of cells (that is, bone marrow cells) that could be removed from the body for gene treatment and then returned to the patient. These two diseases have therefore been among the early objects of attention for researchers designing gene therapy techniques.[23]

In most other cases, it is not practical to remove the target cells (such as brain cells in people with Tay-Sachs disease) for gene repair. A far more promising approach takes advantage of the distinctive properties of different cells, the unique markers each type of cell has on its surface. Once the unique marker for particular cells has been identified, it may be possible to construct a special "package," carrying copies of the normal gene, that will home in on this marker and deliver the new genes exclusively to the cells where the defective gene is active.

Once in the cell, the normal gene may persist as an independent unit, like a plasmid, or may integrate itself randomly somewhere in the DNA. The principal problem is inducing the host cell to produce the proper amount of the desired product.[24] Lack of expression of the normal gene would prevent the "therapy" from being effective, whereas excess production could be deleterious or even fatal. Although transposable elements of the sort that permitted new genetic material to be inserted in a nonrandom fashion and properly expressed in the experiments with fruit flies have not yet been identified in human beings, a comparable set of DNA appears to exist in human beings.

A final worry is that introducing a new gene may disrupt the functioning of the existing cells. For example, were the new piece of DNA to be spliced in the middle of another gene, it could create a gene defect that is worse than the defect the gene therapy was intended to correct.

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[23] Richard Roblin, *Human Genetic Therapy: Outlook and Apprehensions*, in George K. Chacko, ed., HEALTH HANDBOOK, Elsevier-North Holland Pub. Co., New York (1979) at 103, 108-12.

[24] Jean L. Marx, *Still More About Gene Transfer*, 218 SCIENCE 459 (1982).

Despite these technical stumbling blocks, two attempts have already been made at gene therapy. The first—which relied on viral transduction before recombinant DNA techniques were discovered—occurred more than a decade ago and attracted little public attention. Several German sisters had a rare metabolic error that caused them to develop a high level of a substance called arginine in their bloodstream. Left uncorrected, this genetic defect leads to metabolic and neurologic abnormalities, including severe mental retardation. No treatment for argininemia was known, so medical researchers in Germany decided to take advantage of a characteristic of the Shope virus, which, although apparently harmless to human beings, causes people exposed to it to have an unusually low level of arginine. Researchers infected the girls with the virus, in the hope that it would transfer to them its gene for the enzyme that the body needs to metabolize arginine. This attempt to add new genetic material failed—that is, the buildup of arginine continued.[25]

The second attempt at gene therapy in human beings involved a controversial experiment in 1980 on patients suffering from beta-thalassemia. A UCLA physician removed bone marrow cells from a patient in Israel and another in Italy, mixed the cells with DNA coding for hemoglobin (in the hope that a normal hemoglobin gene would be stably incorporated into the bone marrow cells), and then returned the cells to the patients. The attempt apparently neither benefited nor harmed the patients. The investigator justified the experiment on the ground of previous success in transferring foreign genes into the bone marrow of mice. The Institutional Review Board at UCLA—which must give prior approval for research involving human subjects—had refused to give permission to proceed with the experiment on the ground that more animal work was needed.[26] The experiment drew considerable criticism from other scientists, who challenged the adequacy of the animal work.[27] NIH, which had provided the principal investigator

[25] W. French Anderson, *Genetic Therapy,* in Michael P. Hamilton, ed., THE NEW GENETICS AND THE FUTURE OF MAN, William B. Eerdmans Pub. Co., Grand Rapids, Mich. (1972) at 109, 118.

[26] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, PROTECTING HUMAN SUBJECTS, U.S. Government Printing Office, Washington (1981) at 177, 182.

[27] In the opinion of Dr. Bob Williamson, a molecular geneticist at the University of London:

> Cline's experiments were *fundamentally* unethical. His own work on mice shows that there was no basis for hope that globin gene insertion into marrow cells could give clinical benefit at that time. [The subjects'] families were given hope that the gene therapy might help them in their fight for survival.

with funding, imposed sanctions, including stripping him of some of his grant funds.[28] The UCLA experiment generated considerable discussion of the ethical issues involved in gene therapy beyond the facts of that case and particularly about the appropriate time to initiate gene therapy in humans.[29]

Popular notions regarding gene therapy range from seeing it as a weapon for fighting *any* disease to hailing it as a tool for changing human characteristics, including removal of a hypothetical "aggression gene" from hardened criminals. These notions are unrealistic. Many diseases have multigenic or unknown etiologies; human attributes such as kindness or aggression are most certainly the result of a complex interaction of multigenic and environmental factors. The forms of genetic treatment now being discussed would be relevant to such conditions only if the effects of specific genes could be identified and particularly if some of these genes prove to be major determinants, since attempts to change a number of genes at the same time would probably be extremely difficult. It is therefore highly unlikely that in the foreseeable future predictable changes in such attributes could be achieved through genetic alterations.[30]

Gene therapy carried out on somatic cells, such as bone marrow cells, would resemble standard medical therapies in that they all involve changes limited to the cells of the person being treated. They differ, however, in that gene therapy involves an inherent and probably permanent change in the body rather than requiring repeated applications of an outside force or substance. An analogy is organ transplantation, which also involves the incorporation into an individual of cells containing DNA of "foreign" origin.

Germ-Line Cells. Thus far, attempts at gene therapy have focused on treating a discrete population of patients' somatic cells. Some researchers believe that certain forms of gene therapy that have been considered, such as the use of a virus to

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It is unacceptable that patients should be misled in this way. Bob Williamson, *Gene Therapy*, 298 NATURE 416, 418 (1982). *See also*, Nicholas Wade, *UCLA Gene Therapy Racked by Friendly Fire*, 210 SCIENCE 509 (1980).

[28] Marjorie Sun, *Cline Loses Two NIH Grants*, 214 SCIENCE 1220 (1981).

[29] A scientist and an ethicist at the National Institutes of Health suggest that three conditions should be met in animal studies before it is ethical to initiate trials of human gene therapy: (1) the new gene should be put into target cells and remain in them; (2) the new gene should be regulated appropriately; and (3) the presence of the new gene should not harm the cell. W. French Anderson and John C. Fletcher, *Gene Therapy in Human Beings: When is it Ethical to Begin?*, 303 NEW ENG. J. MED. 1293 (1980). *See also*, Arno G. Motulsky, *Impact of Genetic Manipulation on Society and Medicine*, SCIENCE (in press).

[30] Williamson, *supra* note 27.

carry the desired gene to the patient's cells, might also affect germinal cells. Furthermore, gene therapy could also be applied to fertilized human eggs (zygotes) in conjunction with *in vitro* fertilization techniques.[31] Whereas the effects of genetic therapy on somatic cells would be expected to be limited to the individual patient treated, DNA therapy of fertilized eggs would probably affect all cells—including the germ cells—of the developing embryo; assuming normal birth, development, and reproduction, the individual would then pass on the altered gene to his or her offspring according to Mendelian rules. Zygote therapy would thus involve an alteration of the genetic inheritance of future generations and a significant departure from standard medical therapy.

To date, genetic engineering experiments using zygotes have been conducted for academic rather than therapeutic reasons. Several laboratories are currently working on fertilized mouse eggs. In one experiment, mice developed from zygotes injected with the rabbit hemoglobin gene were reported to contain rabbit hemoglobin in their red blood cells.[32] The medical significance is obvious. In a case where both parents are carriers of a particular recessive disorder the risk of an affected child is one in four. But if the relevant normal gene could safely be introduced *in vitro* to a fertilized egg of that couple, the individual who resulted from the egg would not have the disease and none of his or her descendants would be at risk for that disease.

Zygote therapy differs significantly from gene therapy on somatic cells in several ways. First, from the standpoint of the individual it may be useful in the treatment of genetic diseases, like cystic fibrosis, that affect many tissues—lungs, pancreas, intestines, and sex organs—rather than a discrete, accessible subpopulation of cells. Successful treatment at a very early stage of development would confer "good" genes to all the organs of an afflicted individual. Second, from the societal standpoint, such therapy if ever practiced on a vast scale could potentially reduce the overall frequency in the population of genes that usually have deleterious consequences, such as the sickle-cell gene.

Although zygote therapy may hold great promise, it is also fraught with technical risks and uncertainties. First of all, the

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[31] The approach would involve the following: (1) isolating and amplifying the desired gene by standard recombinant DNA techniques, (2) removing a mature ovum from a woman and fertilizing it *in vitro,* (3) injecting copies of the cloned gene into the fertilized egg (zygote) using microsurgical techniques, and (4) implanting the genetically altered zygote into the woman's uterus.

[32] Thomas E. Wagner *et al., Microinjection of a Rabbit B-globin Gene into Zygotes and Its Subsequent Expression in Adult Mice and Their Offspring,* 78 PROC. NAT'L. ACAD. SCI. 6376 (1981).

technique itself is largely unproven, even with laboratory animals. For example, the success rate of microinjecting genes into mouse embryos remains low. Increasing the amount of DNA injected into a zygote makes it more likely that a gene will be incorporated, but it also increases the mortality rate of embryos. Microinjection of DNA into zygotes is obviously not a benign procedure.

The second major technical drawback at present is that transferred genes integrate randomly in the genome. Depending on the site of integration and perhaps the physiological state of the embryo, some of the foreign genes may be expressed and others not. Thus far, in experiments with mice, genes are rarely expressed in a tissue-specific way.[33] Even then, expression of the microinjected foreign gene in somatic tissue has not resulted in stable inheritance of that expression,[34] which is essential if the purpose is to introduce a new trait permanently. The consequences of having the wrong tissues producing the products of inserted genes could be disastrous.[35]

Finally, as in gene therapy on somatic cells, introducing foreign DNA into the zygote may affect the regulation of the cell in some undetermined way. Embryological development depends on a precise set of genetic instructions; disruption of this process is therefore much more likely to have serious adverse consequences than a disruption of the regulatory mechanisms operating in a subset of somatic cells. Instead of being therapeutic, therapy on zygotes or on more-developed embryos might be teratogenic and increase the incidence of congenital abnormalities.

In addition to the technical uncertainties involved, genetic manipulation of embryos raises serious ethical concerns. Altering the human gene pool by eliminating "bad" traits is a form of eugenics, about which there is strong concern. In 1982, the Council of Europe requested "explicit recognition in the European Human Rights Convention of the right to a genetic inheritance which has not been interfered with, except in accordance with certain principles which are recognized as being fully compatible with respect for human rights."[36]

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[33] Ralph L. Brinster *et al., Somatic Expression of Herpes Thymidine Kinase in Mice Following Injection of a Fusion Gene into Eggs,* 27 CELL 223 (1981).

[34] Richard D. Palmiter *et al., Differential Regulation of Metallothionein—Thymidine Kinase Fusion Genes in Transgenic Mice and Their Offspring,* 29 CELL 701 (1982).

[35] Bob Williamson, *Reintroduction of Genetically Transformed Bone Marrow Cells into Mice,* 284 NATURE 397 (1980).

[36] Council of Europe Parliamentary Assembly, 23rd Ordinary Session, *Recommendation 934,* Strasbourg (1982).

Yet the meaning of "respect for human rights" is vague. Some favor gene therapy in embryos because it offers a treatment other than abortion for genetic defects. But—especially in the early years while techniques are being perfected—it would probably be standard practice to examine the genetic and cytologic "health" of any embryos and either not to implant or, if already implanted, to abort any found to be abnormal. Not to do so would risk creating offspring who have genetic problems created by the "therapy" rather than naturally occurring defects.[37]

Furthermore, unless the presence or absence of a genetic defect could be established at a very early stage without harm—that is, at or just prior to fertilization or in a 2 to 4 cell zygote—it would be difficult to determine to whom gene therapy ought to be applied. Yet without such a determination, the use of gene splicing as a "treatment" seems dubious. In most cases identified by genetic screening, both parents are carriers of a recessive condition (those who have only a single defective gene of a pair and do not manifest the disease): in such cases, there is only a 25% chance that the disease is present in any zygote. It would not seem appropriate to run the risk of zygote therapy when three out of four of the potential "patients" do not need treatment.

Therefore, the technical uncertainties, the ethical implications, and the low probability of actually treating an affected person are strong contraindications against therapy of fertilized eggs or embryos becoming a useful clinical option in the near future.

Genes or Genies?

Biotechnology has made rapid advances in the past decade and will most likely continue to be a rapidly unfolding field. The awesome power entailed in these developments can be likened to the genie being let out of the bottle. As one observer of the field has noted:

> Some thirty-five years ago physicists learned how to manipulate the forces in the nucleus of the atom, and the world has been struggling to cope with the results of that discovery ever since. The ability to penetrate the nucleus of the living cell, to rearrange and transplant the nucleic acids that constitute the genetic material of all forms of life, seems a more beneficient power but one that is likely to prove at least as profound in its consequences.[38]

[37] Paul Ramsey, FABRICATED MAN, Yale Univ. Press, New Haven, Conn. (1970) at 75-97.

[38] Nicholas Wade, THE ULTIMATE EXPERIMENT, Walker and Company, New York (1977) at 2.

Stopping any enterprise out of a fear of potential evil not only deprives humanity of the fruits of new findings but also stifles strong impulses for innovation and change. Nevertheless, the technological allure of gene splicing ought not to be allowed to blind society to the need for sober judgments, publicly arrived at, about whether there are instances in which the price of going ahead with an experiment or an innovation will be higher than that paid by stopping the work.[39] In the next two chapters, the Commission examines the issues raised by gene splicing—particularly when used in human therapy—and the mechanisms for monitoring this field.

[39] As Chief justice Burger observed, some of the arguments presented against issuance of a patent for the oil-eating bacteria "remind us that, at times, human ingenuity seems unable to control fully the forces it creates—that with Hamlet, it is sometimes better 'to bear those ills we have than fly to others that we know not of.'" Diamond v. Chakrabarty, 447 U.S. 303, 316 (1980).

Social and Ethical Issues

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The preceding chapters have described the potential benefits of gene splicing, but they have also suggested the awesome and sometimes troubling implications that have shared this technology's spotlight. In this chapter, the Commission considers the social and ethical issues raised as society seeks ways to realize the benefits without incurring unacceptable risks. The Commission has found no ethical precepts that would preclude the initial clinical uses of gene splicing now being undertaken or planned or that would categorically prohibit the research procedures through which knowledge is currently being sought in this important field. But more distant possibilities—either in themselves or in conjunction with other scientific and social developments they may foster—could have less benign effects. Consequently, this Report recommends steps that can and should be taken to keep the social and ethical implications of gene splicing before the public and policymakers as these developments become feasible in the years ahead.

The Commission also believes, for several reasons, that balancing both present and future benefits and risks requires more than a simple arithmetical calculation. First, assessing this new technology through cost/benefit or risk/benefit analysis is complex because decisionmaking about gene splicing technology is characterized by several types and levels of uncertainty. The risks and benefits are poorly conceptualized and understood. Before they can be compared, they must be more clearly distinguished and articulated. Moreover, in many cases consensus—social or scientific—is lacking about whether a particular outcome is in fact a benefit or a detriment. For example, some people regard the prospect of eliminating a genetic disorder in future generations as laudable, while others worry about the unforeseeable consequences of making alter-

ations in germ-line cells. Second, while some people focus on particular consequences of various applications of genetic engineering technology, others are concerned about the acceptability of genetic manipulation per se. In this context, balancing risks against benefits makes little sense because actions, not consequences, are at issue.

In the first part of this chapter, the Commission considers theological and secular attitudes toward the technology as such, rather than toward its possible consequences, and attempts to clarify the nature of these concerns. The Commission then turns to an examination of the types of risks at issue. Although the focus is on spelling out the meaning and significance of certain risks, the benefits being sought through genetic manipulations—and those foregone if progress is thwarted—are also part of the equation.

It should be emphasized that this discussion does not limit itself to concerns about gene splicing that the scientific community or the Commissioners view as valid. Moreover, this chapter is not a comprehensive survey of the social and ethical issues in genetic engineering. Since this Report addresses primarily the potential human uses of gene splicing, there is, for example, no detailed treatment of the subject of laboratory or industrial "biohazards" (that is, the danger of microorganisms to those involved in their creation or manufacture, or to the general public should they escape from a controlled environment). The problems of laboratory hazards and occupational safety have been scrutinized for almost a decade by the United States Congress (through hearings and through studies by the Office of Technology Assessment and the Library of Congress), by RAC, by various bodies at the Federal, state, and local level, and by numerous scientific organizations.[1]

Some of the doubts about the new technology may appear on close examination to be overly speculative or even fanciful. Nonetheless, they have been forcefully expressed in the popular press, by religious writers, and by members of the general public, and they represent important concerns about the responsible exercise of what may prove to be the means by which people achieve freedom from some of the dictates of their genetic inheritance.

The Commission believes it is important for society to address these concerns head-on. If some of these fears prove

[1] Office of Technology Assessment U.S. Congress, IMPACTS OF APPLIED GENETICS—MICRO-ORGANISMS, PLANTS, AND ANIMALS, U.S. Government Printing Office, Washington (1981); Congressional Research Service, Library of Congress, GENETIC ENGINEERING, HUMAN GENETICS, AND CELL BIOLOGY—EVOLUTION OF TECHNOLOGICAL ISSUES, Report Prepared for the Subcomm. on Science, Research and Tech. of the House Comm. on Science and Tech., U.S. Government Printing Office, Washington (1976). *See also* Chapter One *supra,* text accompanying notes 7-15.

groundless, the clearing away of spurious issues will make it easier to focus on any problems of real concern. Without necessarily resolving the problems, the Commission tries to go beyond clarification of the issues to recommend concrete steps for dealing with them.

Concerns About "Playing God"

Hardly a popular article has been written about the social and ethical implications of genetic engineering that does not suggest a link between "God-like powers" and the ability to manipulate the basic material of life. Indeed, a popular book about gene splicing is entitled *Who Should Play God?*[2], and in their June 1980 letter to the President, the three religious leaders sounded a tocsin against the lack of a governmental policy concerning "[t]hose who would play God" through genetic engineering.[3]

Religious Viewpoints. The Commission asked the General Secretaries of the three religious organizations to elaborate on any uniquely theological considerations underlying their concern about gene splicing in humans. The scholars appointed by the organizations to address this question were asked to draw specifically on their particular religious tradition to explain the basis of concerns about genetic engineering; further commentary was provided by other religious scholars.[4]

In the view of the theologians, contemporary developments in molecular biology raise issues of responsibility rather than being matters to be prohibited because they usurp powers that human beings should not possess. The Biblical religions teach that human beings are, in some sense, co-creators with the Supreme Creator.[5] Thus, as interpreted for the Commission by their representatives, these major religious faiths respect and encourage the enhancement of knowledge about nature, as well as responsible use of that knowledge.[6] Endorsement of genetic engineering, which is praised for its potential to

[2] Ted Howard and Jeremy Rifkin, WHO SHOULD PLAY GOD?, Dell Publishing Co., Inc., New York (1977).

[3] *See* Appendix B, pp. 95-96 *infra.*

[4] *See* Appendix D, pp. 107-10 *infra,* for a list of the religious commentators.

[5] Seymour Siegel, *Genetic Engineering*, in PROC. OF THE RABBINICAL ASSEMBLY OF AMERICA, New York (1978) at 164.

[6] In the Biblical tradition of the major Western religions, the universe and all that exists in it is God's creation. In pagan religion, the gods inhabit nature, which is thus seen as sacrosanct, but the Biblical God transcends nature. However, since God created the world, it has meaning and purpose. God has placed a special being on earth—humans—formed in the image of God and endowed with creative powers of intelligence and freedom. Human beings must accept responsibility for the effects brought about by the use of the great

improve the human estate, is linked with the recognition that the misuse of human freedom creates evil and that human knowledge and power can result in harm.

While religious leaders present theological bases for their concerns, essentially the same concerns have been raised—sometimes in slightly different words—by many thoughtful secular observers of contemporary science and technology. Concerns over unintended effects, over the morality of genetic manipulation in all its forms, and over the social and political consequences of new technologies are shared by religious and secular commentators. The examination of the various specific concerns need not be limited, therefore, to the religious format in which some of the issues have been raised.

Fully Understanding the Machinery of Life. Although it does not have a specific religious meaning, the objection to scientists "playing God" is assumed to be self-explanatory. On closer examination, however, it appears to the Commission that it conveys several rather different ideas, some describing the power of gene splicing itself and some relating merely to its consequences.

At its heart, the term represents a reaction to the realization that human beings are on the threshold of understanding how the fundamental machinery of life works.[7] A full understanding of what are now great mysteries, and the powers inherent in that understanding, would be so awesome as to justify the description "God-like." In this view, playing God is not actually an objection to the research but an expression of a sense of awe—and concern.

Since the Enlightenment, Western societies have exalted the search for greater knowledge, while recognizing its awesome implications. Some scientific discoveries reverberate with particular force because they not only open new avenues of research but also challenge people's entire understanding of the world and their place in it. Current discoveries in gene splicing—like the new knowledge associated with Copernicus and Darwin—further dethrone human beings as the unique center of the universe. By identifying DNA and learning how to manipulate it, science seems to have reduced people to a set of malleable molecules that can be interchanged with those of species that people regard as inferior. Yet unlike the earlier

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powers with which they have been endowed—for the betterment of the world—to uncover nature's secrets.

[7] As science journalist Nicholas Wade has observed:

> We are about to enter an explosive phase of discovery in which we are going to reach close to the great goal of Western inquiry: the complete understanding of man as a physical-chemical system.

NOVA, LIFE: PATENT PENDING, WGBH Transcripts, Boston (1982) at 24.

revolutionary discoveries, those in molecular biology are not merely descriptions; they give scientists vast powers for action,

Arrogant Interference with Nature. By what standards are people to guide the exercise of this awesome new freedom if they want to act responsibly? In this context, the charge that human beings are playing God can mean that in "creating new life forms" scientists are abusing their learning by interfering with nature.

But in one sense *all* human activity that produces changes that otherwise would not have occurred interferes with nature. Medical activities as routine as the prescription of eyeglasses for myopia or as dramatic as the repair or replacement of a damaged heart are in this sense "unnatural." In another sense human activity cannot interfere with nature—in the sense of contravening it—since all human activities, including gene splicing, proceed according to the scientific laws that describe natural processes. Ironically, to believe that "playing God" in this sense is even possible would itself be hubris according to some religious thought, which maintains that only God can interfere with the descriptive laws of nature (that is, perform miracles).

If, instead, what is meant is that gene splicing technology interferes with nature in the sense that it violates God's prescriptive natural law or goes against God's purposes as they are manifested in the natural order, then some reason must be

given for this judgment. None of the scholars appointed to report their views by the three religious bodies that urged the Commission to undertake this study suggested that either natural reason or revelation imply that gene splicing technology as such is "unnatural" in this prescriptive sense. Although each scholar expressed concern over particular applications of gene splicing technology, they all also emphasized that human beings have not merely the right but the duty to employ their God-given powers to harness nature for human benefit. To turn away from gene splicing, which may provide a means of curing hereditary diseases, would itself raise serious ethical problems.[8]

Creating New Life Forms. If "creating new life forms" is simply producing organisms with novel characteristics, then human beings create new life forms frequently and have done so since they first learned to cultivate new characteristics in plants and breed new traits in animals. Presumably the idea is that gene splicing creates new life forms, rather than merely modifying old ones, because it "breaches species barriers" by combining DNA from different species—groups of organisms that cannot mate to produce fertile offspring.

Genetic engineering is not the first exercise of humanity's ability to create new life forms through nonsexual reproduction. The creation of hybrid plants seems no more or no less natural than the development of a new strain of *E. coli* bacteria through gene splicing. Further, genetic engineering cannot accurately be called unique in that it involves the creation of new life forms through processes that do not occur in nature without human intervention. As described in Chapter Two, scientists have found that the transfer of DNA between

[8] Pope John Paul II, who had earlier been critical of genetic engineering, recently told a convocation on biological experimentation of the Pontifical Academy of Science of his approval and support for gene splicing when its aim is to "ameliorate the conditions of those who are affected by chromosomic diseases" because this offers "hope for the great number of people affected by those maladies."

> I have no reason to be apprehensive for those experiments in biology that are performed by scientists who, like you, have a profound respect for the human person, since I am sure that they will contribute to the integral well-being of man. On the other hand, I condemn, in the most explicit and formal way, experimental manipulations of the human embryo, since the human being, from conception to death, cannot be exploited for any purpose whatsoever....I praise those who have endeavoured to establish, with full respect for man's dignity and freedom, guidelines and limits for experiments concerning man.

Pope John Paul II, *La sperimentozione in biologia deve contribuire al bene integrale dell'uomo*, L'OSSERVATORE ROMANO, Rome, Oct. 24, 1982, at 2.

organisms of different species occurs in nature without human intervention. Yet, as one eminent scientist in the field has pointed out, it would be unwarranted to assume that a dramatic increase in the frequency of such transfers through human intervention is not problematic simply because DNA transfer sometimes occurs naturally.[9]

In the absence of specific religious prohibitions, either revealed or derived by rational argument from religious premises, it is difficult to see why "breaching species barriers" as such is irreligious or otherwise objectionable. In fact, the very notion that there are barriers that must be breached prejudges the issue. The question is simply whether there is something intrinsically wrong with intentionally crossing species lines. Once the question is posed in this way the answer must be negative—unless one is willing to condemn the production of tangelos by hybridizing tangerines and grapefruits or the production of mules by the mating of asses with horses.

There may nonetheless be two distinct sources of concern about crossing species lines that deserve serious consideration. First, gene splicing affords the possibility of creating hybrids that can reproduce themselves (unlike mules, which are sterile). So the possibility of self-perpetuating "mistakes" adds a new dimension of concern, although here again, the point is not that crossing species lines is inherently wrong, but that it may have undesirable consequences and that these consequences may multiply beyond human control. As noted, the Commission's focus on the human applications of gene splicing has meant that it does not here address this important set of concerns, which lay behind the original self-imposed moratorium on certain categories of gene splicing research and which have been, and continue to be, addressed through various scientific and public mechanisms, such as RAC.[10]

Second, there is the issue of whether particular crossings of species—especially the mixing of human and nonhuman genes—might not be illicit. The moral revulsion at the creation of human-animal hybrids may be traced in part to the prohibition against sexual relations between human beings and lower animals. Sexual relations with lower animals are

[9] Robert L. Sinsheimer, *Genetic Research: The Importance of Maximum Safety and Forethought* (Letter), N.Y. TIMES, May 30, 1977, at A-14.

[10] Despite the great attention paid to the "biohazards" of the research with, and products of, gene splicing, the Environmental Impact Statement filed by NIH on its RAC guidelines focuses on the health effects on humans, plants, and animals and does not deal with ecosystems as entities. Subsequently, however, the Environmental Protection Agency has supported research on the effects of introducing recombinant organisms on the stability of various ecosystems.

thought to degrade human beings and insult their God-given dignity as the highest of God's creatures. But unease at the prospect of human-animal hybrids goes beyond sexual prohibitions.

The possibility of creating such hybrids calls into question basic assumptions about the relationship of human beings to other living things. For example, those who believe that the current treatment of animals—in experimentation, food production, and sport—is morally suspect would not be alone in being troubled by the prospect of exploitive or insensitive treatment of creatures that possess even more human-like qualities than chimpanzees or porpoises do. Could genetic engineering be used to develop a group of virtual slaves—partly human, partly lower animal—to do people's bidding? Paradoxically, the very characteristics that would make such creatures more valuable than any existing animals (that is, their heightened cognitive powers and sensibilities) would also make the moral propriety of their subservient role more problematic. Dispassionate appraisal of the long history of gratuitous destruction and suffering that humanity has visited upon the other inhabitants of the earth indicates that such concerns should not be dismissed as fanciful.

Accordingly, the objection to the creation of new life forms by crossing species lines (whether through gene splicing or otherwise) reflects the concern that human beings lack the God-like knowledge and wisdom required for the exercise of these God-like powers. Specifically, people worry that interspecific hybrids that are partially human in their genetic makeup will be like Dr. Frankenstein's monster. A striking lesson of the Frankenstein story is the uncontrollability and uncertainty of the consequences of human interferences with the natural order. Like the tale of the Sorcerer's apprentice or the myth of the golem created from lifeless dust by the 16th century rabbi, Loew of Prague, the story of Dr. Frankenstein's monster serves as a reminder of the difficulty of restoring order if a creation intended to be helpful proves harmful instead. Indeed, each of these tales conveys a painful irony: in seeking to extend their control over the world, people may lessen it. The artifices they create to do their bidding may rebound destructively against them—the slave may become the master.

Suggesting that someone lacks sufficient knowledge or wisdom to engage in an activity the person knows how to perform thus means that the individual has insufficient knowledge of the consequences of that activity or insufficient wisdom to cope with those consequences. But if this is the rational kernel of the admonition against playing God, then the use of gene splicing technology is not claimed to be wrong as such but wrong because of its potential consequences. Understood in this way, the slogan that crossing species barriers is

playing God does not end the debate, but it does make a point of fundamental importance.[11] It emphasizes that any realistic assessment of the potential consequences of the new technology must be founded upon a sober recognition of human fallibility and ignorance. At bottom, the warning not to play God is closely related to the Socratic injunction "know thyself": in this case, acknowledge the limits of understanding and prediction, rather than assuming that people can foresee all the consequences of their actions or plan adequately for every eventuality.[12]

Any further examination of the notion that the hybridization of species, at least when one of the species is human, is intrinsically wrong (and not merely wrong as a consequence of what is done with the hybrids) involves elaboration of two points. First, what characteristics are uniquely human, setting humanity apart from all other species? And second, does the wrong lie in bestowing some but not all of these characteristics on the new creation or does it stem from depriving the being that might otherwise have arisen from the human genetic material of the opportunity to have a totally human makeup? The Commission believes that these are important issues deserving of serious study.

It should be kept in mind, however, that the information available to the Commission suggests that the ability to create interspecific hybrids of the sort that would present intrinsic moral and religious concerns will not be available in the foreseeable future. The research currently being done on

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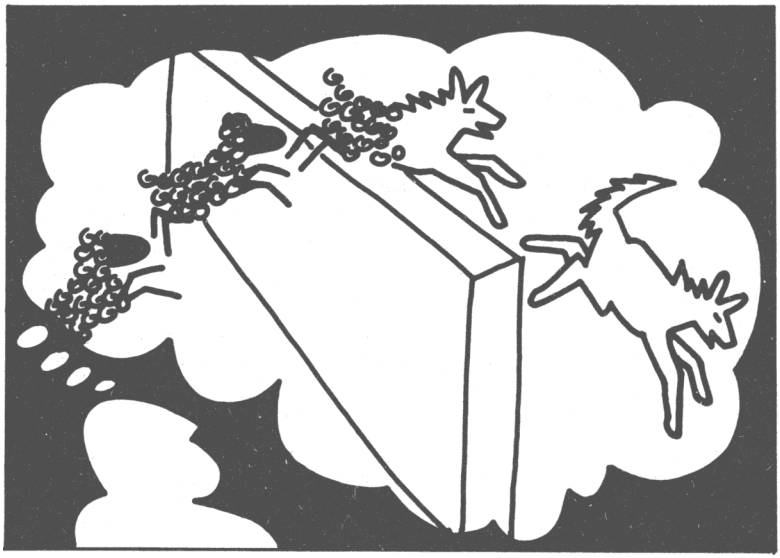
[11] [W]hat made the Gallilean and the other major scientific revolutions disturbing is the reductionism, that we become less than what we are. [T]hat is what is so uncertain about gene therapy, because it gets back to a very fundamental question..."Is there anything unique about humans?"

And if there isn't anything unique about humans, there's nothing wrong with doing gene manipulation. But if there is something unique about humans, then it is wrong to pass over the barrier, wherever the barrier is—but we don't know where the barrier is.

But as soon as you ask, "Where is the barrier?" you ask, "Is there a barrier?" And that's frightening. If there's nothing unique about humans—that's not a theological question but a very real one.

Testimony of Dr. French Anderson, transcript of 22nd meeting of the President's Commission (July 10, 1982) at 115-18.

[12] As one physician-scientist has remarked, "We must all get used to the idea that biomedical technology makes possible many things we should never do." Leon Kass, *The New Biology: What Price Reducing Man's Estate?*, 174 SCIENCE 779 (1971). *See also, Ethical issues in experiments with hybrids of different species,* Appendix I, in Church and Society Office, MANIPULATING LIFE, World Council of Churches. Geneva (1982) at 28.



experimentation with recombinant DNA techniques through the use of single human genes (for example, the insertion of a particular human hemoglobin gene into mouse cells at the embryonic stage) or the study of cellular development through the combining of human genetic material with that of other species in a way that does not result in a mature organism (for example, *in vitro* fusion of human and mouse cells) does not, in the Commission's view, raise problems of an improper "breaching of the barriers."

Concerns About Consequences

To appreciate the complexity of the problem of assessing potential consequences and the individual and societal ability to cope with them, the several types of uncertainty discussed in Chapter One must be considered: the occurrence uncertainty that arises when it is not known whether a particular event will take place (or what sort of future it will take place in), the ethical uncertainty that follows from not knowing whether certain uses of a technology should be regarded as beneficial or harmful, and the conceptual uncertainty that attends new developments that challenge people's fundamental beliefs. The presence of any of these types of uncertainty complicates the task of estimating whether the potential benefits of genetic engineering outweigh the potential risks.

What Are the Likely Outcomes?

Medical applications. Two broad applications may be distinguished: the use of drugs produced by gene splicing (such

as interferon or insulin) and the direct application of gene splicing to human beings through gene therapy or gene surgery.

The problems of personal safety involved in using drugs produced by gene splicing techniques do not appear to be radically different from those that accompany conventionally produced drugs. The basic scientific and ethical issues in this broad area are well known and need not be rehearsed here. The appropriate divisions within the Department of Health and Human Services (in particular, the relevant institutes of the NIH and the Office for Protection from Research Risks, regarding Federally supported research, and the Food and Drug Administration, regarding all drug and vaccine research) need to consider how to apply to genetically engineered drugs the existing mechanisms related to the margin of acceptable risk, the extent and type of animal and human studies required, the standards for manufacturers, and the decision to allow seriously ill patients to opt for more dangerous or less well tested experimental drugs.[13] According to the Department, appropriate steps are already being taken, especially by FDA, to resolve these issues, and the first product of gene splicing has already been approved.[14]

Some direct therapeutic applications of gene splicing technologies to human beings may present distinctive problems of uncertainty not ordinarily encountered in more conventional medical practice. Concern has been expressed that serious harm might result, for example, from a malfunctioning gene inserted by gene therapy. Yet even here the ethical and policy issues do not seem appreciably different from those involved in the development of any new diagnostic and therapeutic techniques. However, in the case of genetic interventions that involve alteration of germ cells, especially stringent animal testing and other precautions are appropriate, since any physicial harms produced might extend to the subject's progeny.

Most experts agree there is a very small likelihood that inheritable changes in germ cells would inadvertently occur when the genetic material of somatic cells is being manipulated. However, the same animal tests and refinements of theoretical models that should precede the use of gene surgery in human beings may shed further light on whether such changes might produce inheritable changes in characteristic functions and whether they will influence germ cells. In both

[13] If there is any special concern in the evaluation of the products of gene splicing, it is only that in the initial stages of any new process there are uncertainties about some effects of the process. For example, bacterial contaminants are a unique by-product of gene splicing and in testing human insulin it was important to determine whether these contaminants induced deleterious antibodies in humans.

[14] *See* note 10, Chapter Two *supra,* and accompanying text.

cases, the resolution of uncertainty depends upon increased understanding of how an inserted gene will perform its function.

Subjects of gene therapy or gene surgery might suffer psychological as well as physical harm. The revelation that a person has a genetic defect or is genetically predisposed to a disease may produce anxiety, fear, or loss of self-esteem—feelings that may be intensified by the belief that the defect is a part of a person's constitution, rather than an outside influence. Similarly, patients might regard alterations of their genes as a more profound change than a surgical procedure or the ingestion of a drug. Experience with genetic screening and counseling suggests that the special significance of a genetic condition to the individual may be accompanied by social stigma based on ignorance, but that efforts to educate individual patients and their families as well as the general public can minimize this problem.[15]

Evolutionary impact on human beings. Some critics warn against the dangers of attempting to control or interfere with the "wisdom of evolution" in order to satisfy scientific curiosity.[16] Those who hold this view object in particular to crossing species lines by gene splicing because they believe that the pervasive inability of different species to produce fertile offspring by sexual reproduction must be an adapative feature, that is, it must confer some significant survival advantage. Thus they view species lines as natural protective barriers that human beings may circumvent only at their peril, although the harm such barriers are supposed to shield people from remains unspecified.

Most proponents of genetic engineering argue that the benefits it will bring are more tangible and important and will affect more people than those objecting suggest. Further, the notion of the "wisdom of evolution" that apparently underlies this consequentialist version of the objection to crossing species lines is not well founded. As the scientific theory of evolution does not postulate a plan that the process of evolution is to achieve, evolutionary changes cannot be said to promote such a plan, wisely or unwisely. Moreover, evolutionary theory recognizes (and natural history confirms) that a "wise" adaptation at one time or place can become a lethal

[15] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, SCREENING AND COUNSELING FOR GENETIC CONDITIONS, U.S. Government Printing Office, Washington (1983).

[16] "Have we the right to counteract, irreversibly, the evolutionary wisdom of millions of years, in order to satisfy the curiosity of a few scientists? The future will curse us for it." Liebe F. Cavalieri. *New Strains of Life--Or Death,* N.Y. TIMES, Aug. 22, 1976 (Magazine), at 8, 68 (quoting Erwin Chargaff).

flaw when circumstances change. So even if it could be shown that species barriers have thus far played an important adaptive role, it would not follow that this will continue. An evolutionary explanation of any inherited characteristic can at most show that having that characteristic gave an organism's ancestors some advantage in enabling them to live long enough to reproduce and that the characteristic has not yet proved maladaptive for the offspring.

Furthermore, as a philosopher concerned with assessing the risks of genetic engineering has recently noted, the ability to manipulate genes, both within and across species lines, may become a crucial asset for survival.

> There may...come a time when, because of natural or man-induced climatic change, the capacity to alter quickly the genetic composition of agricultural plants will be required to forestall catastrophic famine.[17]

The consequentialist version of the warning against crossing species lines seems, then, to be no more a conclusive argument against genetic engineering than the admonition that to cross species lines is wrong because it is playing God. But it does serve the vital purpose of urging that, so far as this is possible, the evolutionary effects of any interventions are taken into account.

One effect that is of particular concern to some observers is the loss of "heterozygote advantage"—the strength (in terms of individual health and species survival) engendered when members of a species have a variety of gene variants rather than all having the same gene. This advantage has two aspects. The first is the protection that varied genes offer for survival of a species in case of a radical change in environment or, more particularly, the occurrence of a novel pathogen. Of course, it would be virtually impossible to know which particular rare gene variant would prove to be valuable under such circumstances. This consideration would favor preserving as much genetic variation as possible, but it would be difficult to weigh this against the benefit to offspring of the variant gene in its homozygous form.

The second aspect is the advantage that may be conferred by a particular gene in past (and present) environments, perhaps accounting for its prevalence in a population. Although the existence of such an advantage could be construed as an argument against making inheritable gene changes, very little is actually known about the existence and nature of such advantages for most genes. The only instance that is widely acknowledged is the advantage, in terms of longevity and

[17] Stephen Stitch, *The Recombinant DNA Debate,* 7 PHIL. & PUB. AFF. 187 (1978).

reproduction, possessed by sickle-cell carriers in tropical regions where malaria has been endemic.[18]

The possible beneficial effects of most gene variants are typically too small to be detected by current research methods—that is, other genetic and environmental effects on the health, longevity, and reproductive history of a population make it difficult to detect whether a particular gene confers any advantage on those who possess it. If it becomes feasible to remove an apparently deleterious gene from a population through routine use of gene surgery, the possible loss of heterozygote advantage will deserve careful evaluation.[19] Population geneticists tend to regard the loss of even minute advantages as serious, since such advantages can confer marked benefits on a species over a great many generations. Medical geneticists, on the other hand, are much less bothered by such losses because they believe that it should be possible to make up, through environmental manipulation (including medical treatment) for the loss of any advantage provided by a variant in any probable future environment.

Will Benefit or Harm Occur?

Parental rights and responsibilities. Current attitudes toward human reproductive activity are founded, in part, on several important assumptions, among them that becoming a parent requires a willingness, within very broad limits, to accept the child a woman gives birth to, that parents' basic duties to children are more or less clear and settled, and that reproduction and parenting are and should remain largely private and autonomous spheres of people's lives. The doors that genetic engineering can open challenge all three of these assumptions.

Genetic counseling and screening have already undercut the first assumption by enabling parents to make an informed decision to prevent the occurrence of some genetic defects by terminating pregnancy, by artificial insemination, or by avoiding conception. If gene therapy or gene surgery become available, parents could have more control over their children's characteristics. They will no longer face the stark alternatives of either playing the hand their child has been

[18] *See* pp. 39-40 *supra.* Carriers of recessive diseases are people who possess one normal and one variant gene, they usually show no deleterious effects and may, as in the case of sickle-cell, have an advantage. The sickle-cell advantage is, however, dependent on time and place. In a temperate, nonmalarial area, or in a tropical climate from which the malaria parasite has been eliminated, carrying the sickle-cell gene would not confer an advantage.

[19] A.M. Capron, *The Law of Genetic Therapy,* in Michael P. Hamilton, ed., THE NEW GENETICS AND THE FUTURE OF MAN, William B. Eerdmans Pub. Co., Grand Rapids, Mich. (1972) at 133, 140 (raising question of a need for a living "genes savings bank").

dealt by the "natural lottery" or avoiding birth or conception. Instead, they could prevent some genetic defects through gene surgery on the zygote and remedy others through gene therapy before the genetic defect produces irreversible changes in the child.

With this increased ability to act for the well-being of the child would come an expansion of parental responsibility. The boundaries of this responsibility—and hence people's conception of what it is to be a good parent—may shift rapidly. It seems safe to say that one important duty of a parent is to prevent or ameliorate serious defects (if it can be done safely) and that the duty to enhance favorable characteristics is less stringent and clear. Yet the new technological capabilities may change people's view of what counts as a defect. For example, if what is now regarded as the normal development of important cognitive skills could be significantly augmented by genetic engineering, then today's "normal" level might be considered deficient tomorrow. Thus ethical uncertainty about the scope of a parent's obligation is linked to conceptual uncertainty about what counts as a defect.

The problem of shifting conceptions of parental responsibility becomes even more complicated when the effects of parents' present actions on descendants beyond their immediate offspring are considered. Deciding whether to engineer a profound change in an expected or newborn child is difficult enough; if the change is inheritable, the burden of responsibility could be truly awesome.

Gene splicing technology may also change people's sense of family and kinship. On the one hand, the possibility of promoting significant inheritable changes through gene surgery may encourage people to think of their family as extending further into the future than they now do. On the other hand, knowing that future generations may employ an even more advanced technology to alter or replace the characteristics passed on to them may weaken people's sense of genetic continuity.

Traditional views of family and kinship associate reproduction with genetic contribution. If genetic engineering makes use of reproductive technologies such as artificial insemination and *in vitro* fertilization, it will increase the strains on this concept of lineage. Whether or not they are accurate, people's beliefs that they are linked to other members of their family by constitutional similarities may play an important role in a family's sense of solidarity and group identity. Knowledge that the genetic link between parents and children is only partial or nonexistent could attenuate these feelings of kinship and family and the sense of continuity and support that they foster. Experience with adoption illustrates successful integration of family members who are not biologically linked. but also

demonstrates the importance some individuals place on an association with biological parents. Here, too, there may be as much uncertainty about whether such changes would be beneficial or harmful as there is about whether they are likely to occur.

Societal obligations. The concept of society's obligation to protect or enhance the health of children and future generations often rests on some notion of an adequate minimum of health care. This benchmark, in turn, depends upon assumptions about what counts as a serious defect or disability, on the one hand, and what constitutes normal functioning or adequate health, on the other. As technological capabilities grow, the boundary between these criteria will blur and shift, and with this will come changes in people's views about what society owes to children and to future generations.

As new technological capabilities raise the standard of normal functioning or adequate health, the scarcity of societal resources may raise anew a very difficult question that theorists of distributive justice have strongly disagreed about: where does justice to future generations end and generosity begin? This question is of vital practical import, for the demands of justice are characteristically thought of as valid claims or entitlements to be enforced by the coercive power of the state, while generosity is usually regarded as a private virtue.

Yet society has traditionally been reluctant to interfere with reproductive choice, at least in the case of competent adults. Even with the advent of genetic counseling and screening, social policy has for the most part scrupulously avoided restricting reproductive choice, either as a matter of justice or on any other grounds.[20] So long as the only alternatives are termination of pregnancy or avoidance of conception, any attempt to enforce a public policy designed to prevent genetic defects constitutes a severe infringement on freedom of reproductive choice. If genetic engineering and related reproductive technologies enable a marked reduction of genetic defects and the burden they impose on their victims and on societal resources, however, mandatory genetic treatments may be advocated. Involuntary blood transfusions of pregnant women have been ordered by courts when physicians conclude this is necessary to prevent serious harm to fetuses. Future developments in gene surgery or gene therapy may lead to further departures from the principle that a competent adult may always refuse medical procedures in nonemergency situations and from the assumption that parenting and reproduction are largely private and autonomous activities.

[20] SCREENING AND COUNSELING FOR GENETIC CONDITIONS, *supra* note 15, at second section of Chapter Two.

The commitment to equality of opportunity. Since the application of the burgeoning recombinant DNA technology will bring benefits as well as costs and since it will be funded at least in part by public resources, it is essential to ask several questions. Who will benefit from the new technology? And will the benefits and costs be distributed equitably?[21] Indeed, what sort of distribution would count as "fair" when the very thing that is being distributed (such as cognitive ability) is itself often the basis for distributing other things of value in society?[22]

The possibilities presented by gene therapy and gene surgery may in fact call into question the scope and limits of a central element of democratic political theory and practice: the commitment to equality of opportunity. One root idea behind the modern concept of equality of opportunity is the belief that because the social assets a person is born with are in no way earned or merited, it is unfair for someone's luck in the "social lottery" to determine that person's most basic prospects in life. Until recently, those who have sought to ground the commitment to equality of opportunity on this belief have only urged that social institutions be designed so as to minimize or

[21] More specifically, it is important to ask whether the further development of gene splicing will reinforce or perhaps exacerbate existing social, cultural, and economic inequalities. This factor explains part of the concern that has been expressed about who will control this technology. Although objections have focused on corporations controlling access (through trade secrets and patents), Howard and Rifkin, *supra* note 2, at 189-207, the greatest abuses of genetics have involved governmental decisionmaking. Kenneth M. Ludmerer, GENETICS AND AMERICAN SOCIETY: A HISTORICAL APPRAISAL, Johns Hopkins Univ. Press, Baltimore (1972) at 121-34.

[22] Suppose, for example, a society distributes certain scarce resources on the basis of merit—*e.g.,* intelligence, diligence, physical abilities. What if intelligence could be engineered upward? Who would merit this increase in merit? The very oddity of the inquiry calls into question the continued use of intelligence as a basis for resolving competing claims—say, for admission to educational institutions or for access to the intelligence-raising technology itself. We could resort to the other coexisting merit attributes—unless they too were alterable by design. Under these conditions, how could we retain our system of merit distribution? If we could not, how would we then distribute the resources? By resort to a standard of efficiency? By leaving matters to a market? Or by designing a lottery?

Michael H. Shapiro, *Introduction to the Issue: Some Dilemmas of Biotechnology Research,* 51 S. CAL. L. REV.. 987, 1001-02 (1978) (citations omitted).

compensate for the influence that the "social lottery" exerts on a person's opportunities.[23] Genetic engineering raises the question of whether equality of opportunity requires intervention in the "natural lottery" as well, for people's initial genetic assets, like their initial social assets, are unearned and yet exert a profound influence on opportunities in life. Even to ask this question challenges a fundamental assumption about the scope of principles of distributive justice, namely that they deal only with inequalities in social goods and play no role in regulating natural inequalities.

Genetic malleability and the sense of personal identity. The manipulation of genes that play an important role in regulating processes of growth and aging or that contribute significantly to personality or intelligence—if it ever becomes possible—could have considerable impact on the way people think of themselves. The current tendency is to think of a person as an individual of a certain character and personality that, following the normal stages of physical, social, and psychological development, is relatively fixed within certain parameters. But this concept—and the sense of predictability and stability in interpersonal relations that it confers—could quickly become outmoded if people use gene splicing to make basic changes in themselves over the course of a lifetime. People can already be changed profoundly through psychosurgery, behavior modification, or the therapeutic use of psychoactive drugs. But genetic engineering might possibly provide quicker, more selective, and easier means. Here again, uncertainty about possible shifts in some of people's most basic concepts brings with it evaluative and ethical uncertainty because the concepts in question are intimately tied to values and ethical assumptions. It is not likely that anything so profound as a change in the notion of personal identity or of normal stages of development over a lifetime is something to which people would have clear value responses in advance.

Changing the meaning of being human. Some geneticists have seen in their field the possibility of benefit through improving human traits.[24] Human beings have the chance to

[23] John Rawls, A THEORY OF JUSTICE, Harvard Univ. Press, Cambridge, Mass. (1973) at 83.

[24] Herman J. Muller is the scientist most associated with this view. In the mid-1960s he viewed selective breeding as a method for "a much greater, speedier, and more significant improvement of the population" than any direct rearrangement of genetic material possible in the 21st century. He advocated giving women "germinal choice" through artificial insemination of them with the genes for superior traits. Herman J. Muller, *Means and Aims in Human Genetic Betterment,* in T.M. Sonneborn, ed., CONTROL OF HUMAN HEREDITY AND EVOLUTION, Macmillan Co., New York (1965) at 100. The list of the traits found desirable by Professor Muller changed dramatically over time, as did the types of individuals whose sperm should be used--Lenin appeared

"rise above [their] nature" for "the first time in all time," as one leader in the field has observed:

> It has long been apparent that you and I do not enter this world as unformed clay compliant to any mold. Rather, we have in our beginnings some bent of mind, some shade of character. The origin of this structure—of the fiber in this clay—was for centuries mysterious....Today...we know to look within. We seek not in the stars but in our genes for the herald of our fate.[25]

Will gene splicing actually make possible such changes in "human nature" for the first time? In some ways this question is unanswerable since there is great disagreement about which particular characteristics make up "human nature." For some people, the concept encompasses those characteristics that are uniquely human. Yet most human genes are actually found in other mammals as well; moreover, recent work by ethologists and other biologists on animal behavior and capacities is demonstrating that many characteristics once regarded as unique to human beings are actually shared by other animals, particularly by the higher primates, although an ability to record and study the past and to plan beyond the immediate future appears to be a singularly human trait.

Other people regard the critical qualities as those natural characteristics that are common to all human beings, or at least all who fall within a certain "normal range." "Natural" here means characteristics that people are born with as opposed to those that result from social convention, education, or acculturation.

To consider whether gene splicing would allow the changing of human nature thus breaks down into two questions. Which characteristics found in all human beings are inborn or have a large inborn basis? And will gene splicing techniques be able to alter or replace some of the genetic bases of those characteristics? As to the first, the history of religious, philosophical, and scientific thought abounds with fundamental disputes over human nature. Without a consensus on that

on the first list but disappeared during the Cold War. Garland E. Allen, *Science and Society in the Eugenic Thought* of *H.J. Muller,* 20 BIOSCIENCE 346 (1970).

[25] Robert L. Sinsheimer, *The Prospect of Designed Genetic Change,* 32 ENGINEERING AND SCIENCE 8, 13 (April 1969). Prof. Sinsheimer took a different view from Prof. Muller. He contrasted the "older eugenics" of breeding, which would require a "massive social program," with the new eugenics that could permit "conversion of all the unfit to the highest genetic level" and "could, at least in principle, be implemented on a quite individual basis, in one generation, and subject to no existing social restrictions." Id. Prof. Sinsheimer subsequently became very doubtful about the wisdom of changing genes. *See* note 19, Chapter One *supra.*

issue the second question could only be answered affirmatively if it were clear that gene splicing will eventually allow the alteration of all natural characteristics of human beings.

As it is by no means certain that it will ever be possible to change the genetic basis of all natural characteristics, it seems premature to assume that gene splicing will enable changes in human nature. At most, it can perhaps be said that this technology may eventually allow some aspects of what it means to be human to be changed. Yet even that possibility rightly evokes profound concern and burdens everyone with an awesome and inescapable responsibility—either to develop and employ this capability for the good of humanity or to reject it in order to avoid potential undesirable consequences.

The possibility of changing human nature must, however, be kept in perspective. First, within the limits imposed by human beings' genetic endowment, there is already considerable scope by means other than gene splicing for changing some acquired characteristics that are distinctively human. For example, people's desires, values, and the way they live can be changed significantly through alterations in social and economic institutions and through mass education, indoctrination, and various forms of behavior control. Thus, even if gene splicing had the power that some people are concerned about, it would not be unique in its ability to produce major changes in what it means to be human—although it would be unusual in acting on the inheritable foundation of thoughts and actions. If the technology can ever be used in this way, the heritability of the changes ought probably to regarded as significantly different from any changes now possible.[26]

Second, according to the theory of evolution, the genetic basis of what is distinctively human continually changes through the interplay of random mutation and natural selection. The concern, then, is that gene splicing will for the first

[26] If any one age really attains, by eugenics and scientific education, the power to make its descendants what it pleases, all men who live after it are patients of that power. They are weaker, not stronger: for though we may have put wonderful machines in their hands we have pre-ordained how they are to use them....The real picture is that of one dominant age...which resists all previous ages most successfully and dominates all subsequent ages most irresistibly, and thus is the real master of the human species. But even within this master generation (itself an infinitesimal minority of the species) the power will be exercised by a minority smaller still. Man's conquest of Nature, if the dreams of the scientific planners are realized, means the rule of a few hundreds of men over billions upon billions of men.

C.S. Lewis, THE ABOLITION OF MAN, Collier-Macmillan, New York (1965) at 70-71.

time allow deliberate, selective, and rapid alterations to be made in the human genetic constitution.

Finally, concern about changing human nature may at bottom be still more narrowly focused upon those characteristics of human beings—whether unique to the species or not—that are especially valued or cherished. Here, too, there may be disagreement as to which characteristics are most valuable and the value of a given characteristic may depend upon the social or natural environment in which it is manifested.

In sum, the question of whether gene splicing will enable changes in human nature—and the ethical, social, and philosophical significance of such changes—cannot be determined until much more is known about human genetics, specifically the exact contribution of heredity to many human physical and, more important, behavioral traits. Indeed, one of the most important contributions genetic engineering could make to the science of behavioral genetics may be that it will help resolve the age-old controversy of nature versus nurture. If designed changes were possible, society would have to confront whether such changes should be made, and, if they should, which ones. The problems created by uncertainty are particularly notable here since any decision about what characteristics are "desirable" would depend on the world that people will be living in, which is itself unknowable in advance.

Unacceptable uses of gene splicing. A recent National Science Foundation survey indicates that though Americans are generally against restrictions on scientific research, "a notable exception was the opposition to scientists creating new life forms." The survey notes that

> Almost two thirds of the public believe that studies in this area should not be pursued. Fear of the unknown and of possible misuse of the discoveries by some malevolent dictator are among the reasons that could be given for opposition to such genetic engineering.[27]

Given the excesses of the eugenics movement in the United States and elsewhere in the early decades of this century and the role of eugenic theory in mass atrocities perpetrated by the Nazis, these fears cannot be dismissed as groundless. Some comfort may be drawn from the fact that although the possibility of directing human inheritance through simple breeding techniques has existed for centuries, it has not, with relatively minor exceptions, been attempted. Furthermore, the peculiar social and political circumstances that led to these attempts to control human reproduction through the coercive

[27] John Walsh, *Public Attitude Toward Science Is Yes, but-*, 215 SCIENCE 270 (1982) (quoting National Science Foundation, Science Indicators 1980).

power of the state are not present in this country and are unlikely to occur in the foreseeable future.

Reassuring though they are, these answers are far from conclusive. Government control of sexual reproduction on a broad scale—through an enforced scheme for mating human beings—would require enormous repressive power and social control over individuals over an extended period of time. What might prove more tempting to a dictator or authoritarian ruling elite is the possibility of scientists rapidly making major changes in the genetic composition of a small group in the privacy of the laboratory.

Though there appears at present to be no evidence that the government of this or any other country is attempting to use gene splicing for unacceptable political purposes, the Commission believes that the appropriate posture for the public and the scientific community is one of vigilance. The best safeguards against such abuses are a continued support of democratic institutions and a commitment to individual rights combined with public education about the actual and potential uses of gene splicing technology. Of course, such efforts in this country would not avoid undesirable uses of genetic engineering by totalitarian governments, unless they led to effective international restrictions.[28]

A more subtle danger is that if genetically engineered changes ever become relatively easy to make, there may be a tendency to identify what are in fact social problems as genetic deficiences of individuals or to assume that the appropriate solution to a given problem, whether social or individual, is genetic manipulation.[29] The relative ease of genetic methods (if

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[28] Another misuse of gene splicing with international ramifications, described by the World Council of Churches as a "grave hazard," is "the deliberate production of pathogenic micro-organisms for biological warfare or terrorism." Paul Abrecht, ed., 2 FAITH AND SCIENCE IN AN UNJUST WORLD: REPORT OF THE WORLD COUNCIL OF CHURCHES' CONFERENCE ON FAITH, SCIENCE AND THE FUTURE, Fortress Press, Philadelphia (1980) at 53.

[29] "In discussing the use of any science, including genetics, to solve social problems, it...becomes important to demarcate clearly the *limit* that scientific technique may be expected to contribute to an effective solution." Ludmerer, *supra* note 21, at 180. To take an extreme example, in a society in which gene surgery was widely used and accepted, it might be tempting to "solve" the problem of racial discrimination by making genetic changes to eliminate dark skin. A less fanciful example would be the decision to make genetic alterations in certain groups of workers who are exposed to dangerous chemicals in the workplace rather than to eliminate the dangers.

> Moreover, genetic research may denigrate the value that society has perceived in the moral and autonomous aspects of human conduct by forcing society to question the limits of free

gene therapy becomes an accepted medical technique) should most certainly not draw attention away from the underlying social causes of such problems.

Distributing the power to control gene splicing. Beyond any fear of the malevolent use of gene splicing, attention must be paid to a more basic question about the distribution of power: who should decide which lines of genetic engineering research ought to be pursued and which applications of the technology ought to be promoted?

This question is not ordinarily raised about medical technology in general. When it is, the assumption is that for the most part the key decisions are to be made by the relevant experts, the research community, and the medical profession, guided by the availability of research funds (which come predominately from Federal agencies) and by the dictates of medical malpractice law and of state and Federal regulatory agencies designed to protect the public from very tangible, unambiguous harms. Yet genetic engineering is more than a new medical technology. Its potential uses, as discussed, extend far beyond intervention to cure or prevent disease or to restore functioning. This more expansive nature makes it unlikely that decisions about the development of gene splicing technology can be made appropriately within institutions that have evolved to control medical technology and the practice of medicine.

Clearly, adequate institutional arrangements for decision-making about the further development of gene splicing technology must assign a substantial role to experts in the field. Yet it is important to understand the unavoidable limitations of technical expertise. On the one hand, there are the limitations of the experts' knowledge, on the other, there are the limitations of technical knowledge itself, no matter how thorough. Experts in genetic engineering can provide the most accurate available data, from which probability statements can be formulated. But neither geneticists nor scientists experienced in risk assessment have any special expertise about evaluative and conceptual uncertainties. An expert might conclude that there is a 5% probability that a certain harmful outcome will occur, but that knowledge is not sufficient for deciding whether such a probability is an acceptable degree of risk. Nor can scientific expertise answer the question of whether the burdens of risk would fall disproportionately upon some people,

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> will and self-determination. Thus, genetic research has the power to reorder society's priorities and restructure its values; fundamentally, it can change the structures of human thought and the social construction of reality.

Marc Lappé and Patricia Archbold Martin, *The Place of the Public in the Conduct of Science,* 52 S. CAL. L. REV. 1535, 1537 (1978) (citations omitted).

for this is a moral, not a scientific, question. This is not to say, of course, that scientific experts should not make moral judgments or that if they do they ought to be ignored. But the limitations of expertise must be clearly understood.

In general the public can reasonably rely on the judgments of experts in the field to the extent that at least three conditions are satisfied: (1) there is a strong consensus among the experts, (2) the process by which individuals come to be identified as experts is not unduly influenced by political factors or other forces unrelated to their qualifications as experts, and (3) the experts are not subject to serious conflicts of interest that are likely to distort their judgments or to make their advice unreliable.[30] Whether, or to what extent, these conditions are satisfied cannot be answered once and for all. Instead, they must be viewed as useful rules-of-thumb for assessing and reassessing the role of experts in the formation of responsible public policy.

Commercial-academic relations. Concern over the latter two points—unacceptable uses of the technology and the power of control it—have contributed to a growing public debate about the increased commercial involvement with university-based research on gene splicing. Constraints on support for basic science research by the Federal government in the past decade have been compounded by economic problems that have reduced both state budgets for higher education and the grants of philanthropic foundations. Consequently, academic research scientists are turning increasingly to industry,[31] forming ties that have raised concern about how to accommodate the divergent goals and norms of science and industry.

Universities have historically been dedicated to increasing the general fund of knowledge through basic research, the open exchange of information and ideas, and the training of new researchers and scholars. These goals may run headlong into those of industry—the development of marketable products and techniques through applied research by maintaining a competitive posture, protecting trade secrets, and seeking patent protection.

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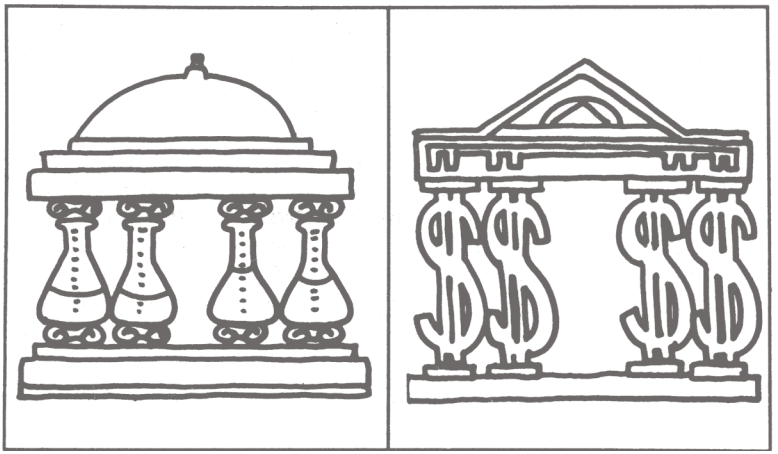
[30] *See* Stitch, *supra* note 17.

[31] Estimates have put industry support of academic research at about $200 million per year. Although this represents only about 4% of what government contributes, it is a growing proportion. The formation in the past decade of about 200 new private ventures to pursue research and development in genetic engineering has been paralleled by increased interest on the part of existing industrial firms in universities that have strong programs in molecular biology. This interest has been capped by several well publicized multimillion dollar agreements.



The conflicts occasioned by these developments are not unique to genetic engineering, indeed, at the beginning of this century a number of expanding universities shifted their focus from the traditional arts and sciences as they became allied with the burgeoning electrical and chemical industries. Medicine, agriculture, econometrics, solid state physics, and computer science have all been advanced in part because of combined forces of industry and universities. Yet the recent similar developments in biotechnology present these issues in sharper relief for several reasons.

First, commercialization of biotechnology seems to be proceeding more rapidly than in chemistry and physics. And in gene splicing, the gap between theory and application—between a graduate student's work in the lab and a highly lucrative product—is often quite small. Finally, the range of potential applications of the research is very broad.

Increased private funding for bioengineering research has therefore sparked questions about conflicts of interest and about the impact of commercialization on academe more generally.[32] Some see these issues as private concerns relating only to the particular universities and firms contracting with each other, a view reflected at a recent conference at Pajaro Dunes when university officials and industry representatives

[32] That journey of discovery can only be undertaken once, and it would be better undertaken by people who have no interest in anything other than discovering the truth, whose hands are clean, whose motives can never be criticized. That's in the public's interest; that is in science's true interest. And if the commercialization, if this secondary goal of getting rich, ever starts to influence a scientist's primary goal, a university's primary goal of discovering the truth, then the scientists themselves, I hope, will have the sense to put a halt to it.

Wade, *supra* note 7, at 24-25.

met in private to discuss concerns about commercialization. The participants at this privately funded conference of 5 leading universities and 11 corporations issued a statement intended to "get some general principles on the record" and "set an agenda for further discussion of the issues." The document raised questions of contract review and disclosure, exclusive licensure, and conflicts of interest encountered by university and faculty. It encouraged university faculties to continue examination of these issues over which commentators have noted that "[p]luralism and a certain measure of confusion prevail."[33]

Other issues are also at stake: Can professional virtue be maintained in the face of considerable financial temptations? How will private funding change professors' outlooks?[34] Will fewer be interested in teaching undergraduates? Will they encourage graduate students to focus on projects with maximum commercial potential, instead of those that would foster a more well rounded background? Will commercialization effect a shift from basic to applied research and, if so, with what consequences? Will the secrecy required by industry impede the free exchange of scientific information? What about conflicts of interest when the same academic department includes owners or employees of competitive bioengineering ventures? Will academic appointments and promotions be skewed to favor those who can attract private research funds to the university?

The Association of American Universities has recently suggested that it become a clearinghouse for information on commercialization.[35] These and related questions have also been the subject of debate in the press and before Congressional committees. Undoubtedly, such concerns spill over into the public arena when the question is whether the new agreements are "skimming off the cream produced by decades of taxpayer

[33] Barbara J. Culliton, *Pajaro Dunes: The Search for Consensus,* 216 SCIENCE 155 (1982); Draft Statement Pajaro Dunes Conference (March 25-27, 1982).

[34] One physician-scientist who formerly held high budgetary and science advisory positions in the Federal government and who is presently the Dean of a school of public health has suggested that the financial agreements between universities and medical school faculty in the clinical departments could be "at least partially relevant" in finding a means of protecting the research and educational commitments of the basic-science faculties while generating added income. Gilbert S. Omenn, *Taking University Research into the Marketplace,* 307 NEW ENG. J. MED. 694, 699-700 (1982).

[35] Letter from Robert M. Rosenzweig, chairman of the Association of American Universities Committee on University/Industry Relations, to Reps. Don Fuqua and Albert Gore, Jr. (Oct. 28, 1982) (on report of AAU study group).

funded work," as Rep. Albert Gore, Jr., put it in opening Congressional hearings on the subject.[36] Only a continuing public debate over these as-yet-unresolved questions on the commercialization of biotechnology can ensure that the public's interests are being met—its interest in the integrity and credibility of scientific research, in a sound and balanced research agenda, and in the wise expenditure of Federal research dollars.

Continuing Concerns

A distinction has been drawn in this Report between two views: (1) that gene splicing technology is intrinsically wrong or contrary to important values and (2) that, while the technology is not inherently wrong, certain of its applications or consequences are undesirable. Regarding the latter, it has also been noted that genetic engineering involves an array of uncertainties beyond those usually found in technological developments. Not only is the occurrence of specific desirable or undesirable consequences impossible to predict but the application of gene splicing could have far-reaching consequences that could alter basic individual and social values.

The Commission could find no ground for concluding that any current or planned forms of genetic engineering, whether using human or nonhuman material, are intrinsically wrong or irreligious per se. The Commission does not see in the rapid development of gene splicing the "fundamental danger" to world safety or to human values that concerned the leaders of the three religious organizations.[37] Rather, the issue that deserves careful thought is: by what standards, and toward what objectives, should the great new powers of genetic engineering be guided?

Even though the many issues raised by gene splicing in human beings need to be considered one by one if their potential consequences are to be clearly assessed, it would be a mistake to compartmentalize the issues.[38] Although the

[36] *Commercialization of Academic Biomedical Research,* Hearings before the Subcomm. on Invest. and Oversight and the Subcomm. on Science, Research and Tech. of the House Comm. on Science and Tech., 97th Cong., 1st Sess., June 8, 1981, at 2.

[37] *See* Appendix B, pp. 95-96 *infra.*

[38] The predominant methodological strategy of biological research is reductionism: the isolation of the phenomenon under study from its usual circumstances, thereby reducing the number of variables that affect the analysis. This allows a clearer understanding of the "basic" processes, and has led to important discoveries.

The strength of reductionism is the principle of isolation. This principle, however, is also inherently limiting: the circum-

Commission has not found any ethical, social, or legal barriers to continued research in this field, there remains an important concern expressed by the warning against "playing God." It not only reminds human beings that they are only human and will some day have to pay if they underestimate their own ignorance and fallibility; it also points to the weighty and unusual nature of this activity, which stirs elusive fears that are not easily calmed.

At this point in the development of genetic engineering no reasons have been found for abandoning the entire enterprise—indeed, it would probably be naive to assume that it could be. Given the great scientific, medical, and commercial interest in this technology, it is doubtful that efforts to foreclose important lines of investigation would succeed. If, for example, the United States were to attempt such a step, researchers and investment capital would probably shift to other countries where such prohibitions did not exist. To expect humanity to turn its back on what may be one of the greatest technological revolutions may itself betray a failure to recognize the limits of individual and social self-restraint. Even if important lines of research in this country or elsewhere could be halted, to do so would be to run a different sort of risk: that of depriving humanity of the great benefits genetic engineering may bring.

Assuming that research will continue somewhere, it seems more prudent to encourage its development and control under the sophisticated and responsive regulatory arrangements of this country, subject to the scrutiny of a free press and within the general framework of democratic institutions. In light of the potential benefits and risks—uncertain though they may be at this point—a responsible social policy on genetic engineering requires the cooperation of many institutions and organizations.

> stances of the investigation are necessarily "unreal" in everyday terms. Of course, it may be that the isolated phenomena behave similarly under natural circumstances. This assumption, however, is often uncertain and may frequently be untrue. Moreover, the characteristics of those natural circumstances are rarely fully known. In some cases, knowledge of the multiple external influences upon biological processes could lead to a perception of those processes quite different from those obtained in the isolation of laboratory study. A critical understanding of present biological knowledge requires recognition of those methodological weaknesses. Public participation in science, by broadening the range of factors considered at each stage of investigation, provides a means of counteracting biases resulting from reductionist strategy.

Halsted R. Holman and Diana B. Dutton, *A Case for Public Participation in Science Policy Formation and Practice.* 51 S. CAL. L. REV. 1505, 1513-14 (1978) (citation omitted).

Efficient regulation and oversight will require considerable division of responsibility among different bodies and agencies. Legal controls will necessarily focus on the prevention of tangible harms to individuals and the environment. Nonetheless, the Commission believes it is crucial that those entrusted with such oversight and regulation do not lose sight of the more elusive, but equally important, concerns about the human significance of genetic engineering or neglect such concerns because they do not fit neatly into existing institutional jurisdictions. The continued development of gene splicing approved in this Report will require periodic reassessment as greater knowledge is gained about the ethical and social, as well as the technical. aspects of the subject.

Protecting the Future

4

The material presented in the earlier chapters provides the basis for the Commission's recommendations on the means through which the issues generated by genetic engineering can continue to receive appropriate attention. These issues are not matters for a single day, deserving of only occasional attention. They will be of concern to the people of this country—and of the entire globe—for the foreseeable future; indeed, the results of research and development in gene splicing will be one of the major determinants of the shape of that future. Thus, it is important that this field, with its profound social and ethical consequences, retain a place at the very center of "the conversation of mankind."[1]

Specifically, in the preceding material the Commission has seen that:

(1) The careful attention paid by scientists, private groups, and government officials to the immediate health and environmental risks has been rewarded with a record of safe and fruitful research and development.

(2) Although the Federal Interagency Committee on Recombinant DNA Research has been inactive for several years, the Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health (NIH) has provided an informal means for intragovernmental communication, as well as overseeing the safety of NIH-funded research.

(3) The issues raised by the projected human uses of gene splicing, which heretofore have not received

[1] Michael Oakeshott, *The Voice of Poetry in the Conversation of Mankind*, in RATIONALISM IN POLITICS AND OTHER ESSAYS, Metheun, London (1962) at 197.

attention, are as at least as complex and important as those addressed by RAC thus far.

(4) These issues would benefit from an evaluation process that is continuing rather than sporadic, to allow a review body to develop coherent standards and orderly procedures, while making provisions for unexpected developments in gene splicing and other changes in the world at large.

(5) It would be desirable to develop means for such an evaluation process now, not because of any threat of imminent harm but because the issues are better addressed in anticipation rather than in the wake of a possible untoward or unforeseen outcome.

(6) The issues are so wide-ranging as to require a process that is broad-based rather than primarily expert, since the issues cannot be resolved on technical grounds alone and since many of the most knowledgeable scientists are deeply involved in the field as researchers or even as entrepreneurs.

These observations do not, of course, point to any single framework for a continuing oversight of this area. Because of its large role in funding biomedical research and its statutory responsibilities to ensure that environmental, industrial, and pharmaceutical safety standards are being met, the Federal government will be a participant in any well-designed process of planning and review. But this function need not be regarded as exclusively governmental. A variety of organizations in the private sector—such as the American Association for the Advancement of Science, the National Academy of Sciences, the Industrial Biotechnology Association, and the Pharmaceutical Manufacturers Association—could well play important leadership and educational roles.

Finally, within the governmental sector, the responsibility for oversight—not only coordinating what is being done but also identifying what still needs to be done—is very important. It, too, can be supplied by a variety of means, including Congressional committees and the Office of Technology Assessment. Or the body charged with overall responsibility might also have direct regulatory power, as opposed to the authority to stimulate appropriate actions on the part of those agencies that do have the power.

Objectives

The President's Commission believes that the design of any oversight group should be guided by several objectives. First, the group should regard education as a primary responsibility. It is necessary to educate the scientific community about

the social and ethical implications of its work as well as to educate the public about science.

Second, the group should have roles both of general oversight and of leadership within the Federal government. For this, it will need direct access, through liaison arrangements, to all Federal departments or agencies with a large stake in sponsoring, regulating, or scrutinizing work in this field. At a minimum it should possess "action-forcing power," whereby departments and agencies are required to publish its regulatory recommendations for comment in the *Federal Register* within a specified time and then either to adopt or reject the recommendations, with an explanation likewise published in the *Federal Register*.

Third, the body should be capable of leading, as well as reflecting, public thinking on the important issues before it, it can serve as an intermediary between biomedical scientists and the public, helping to translate and clarify the ideas and concerns of each for the other. To do so, it will need diverse membership.[2] It also ought to conduct its work in public and seek to have it widely disseminated. A policymaking process that draws on nonscientists and avoids unnecessary secrecy is

[2] One well-known investigator has urged: "If this investigation [work in genetic engineering] is done with man, the study should be made with collaborators who can protect genetics from public scorn by having scientists working with articulate sociologists and psychologists who plan for a long time before doing the engineering."

Kenneth M. Ludmerer, GENETICS AND AMERICAN SOCIETY: A HISTORICAL APPRAISAL, Johns Hopkins Univ. Press, Baltimore (1972) at 179 (quoting Dr. Clarence P. Oliver).

likely not only to lead to better results but also to inspire much greater public confidence in, and support for, research efforts themselves.[3]

Fourth, it should strive to operate on scientifically sound premises. For this it will need a means of drawing on groups of scientists for advice and explanation in a way that does not lead it to be dominated by the scientific community.

Fifth, it should treat—in as unified a framework as possible—all the issues raised by genetic engineering: laboratory and industrial safety, environmental hazards, agricultural and commercial opportunities and pitfalls, international ramifications, biomedical benefits and risks, and social and ethical implications.

Sixth, insofar as possible, the oversight functions should be separated from any sponsoring functions, so that no conflicts of interest, of the sort that plagued the Atomic Energy Commission, will arise.

Revising RAC

RAC, which had been created in October 1974 as a scientific and technical committee, was subsequently made into a more representative body by HEW Secretary Joseph Califano, through the addition of nonscientific members of the

[3] If this industry follows the path that appears easier initially, the cloistered avoidance of other forces of society, it will pay a penalty years hence should some event force a public inquiry. George E. Brown, Jr., *The Policymaking Challenge of the Bioengineering Industry,* 4 RECOMBINANT DNA TECHNICAL BULL. 121, 123 (1981). Rep. Brown, former chairman of the House Subcommittee on Science, Research and Technology, has urged the commercial concerns in the genetic engineering field to establish public trust by forming an "active" and "open" industrial council to exercise powers of censure, laboratory approval, and similar functions. *Id.* at 122.

> But there needs to be a broader entity, at least initially. There should be a council with a broad and diverse membership to look at the entire range of issues that a genetic engineering industry raises. Scientists, lay people, lawyers, policymakers, regulators, clergy, and other groups should be represented in a council of manageable size....There will be objections to the inclusion of nonscientists on the panel deciding scientific matters. These have been heard before but experience has shown that these people become valuable contributors.
>
> . . . Knowing the aversion that researchers have to being burdened by broad social and ethical considerations, I would understand a reluctance by researchers to willingly submit to what would undoubtedly be a time consuming discussion. But these views will be present in any public debate and are better incorporated sooner than later.

Id. at 123.

public. Recently, Dr. Donald Fredrickson, who presided over the transformation as the Director of NIH, suggested that the time for a "third generation" RAC may have arrived.[4] The President's Commission concurs, since there is plainly great value in building on the history—largely regarded as successful—of RAC. Design of an appropriate body for the task will require consideration of many factors, some of which (such as funding) are beyond the purview of the President's Commission.[5] But as a starting point, it may be helpful if the Commission suggests possible formats for consideration by the President and Congress.[6]

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[4] Joseph G. Perpich, *Industrial Involvement in the Development of NIH Recombinant DNA Research Guidelines and Related Federal Policies*, 5 RECOMBINANT DNA TECHNICAL BULL. 59, 77 (1982) (quoting a talk by Dr. Fredrickson, *rDNA Controversy: The NIH Viewpoint*, delivered at the annual meeting of the American Association for the Advancement of Science, Jan. 7, 1982, to be published in a volume edited by Raymond Zalinskas and Burke Zimmerman).

> The idea...is to make RAC more representative of both the scientific and regulatory communities as well as the public to be better equipped to deal with the emerging problems and be relieved of some of the detailed burden of reviewing minor administrative concerns. Such a "third generation" RAC should be accountable to a Cabinet officer.. .
>
> The concept was instantly adopted, at least in principle, by Dr. Ray Thorton, chairman of RAC and a fellow panelist at AAAS.

"Third Generation" of RAC Suggested by Dr. Fredrickson, 2 GENETIC ENGINEERING LETTER 1 (1982).

[5] In Diamond v. Chakrabarty, 447 U.S. 303 (1980), the Supreme Court reached a similar conclusion about the competence of the judiciary to decide, within the context of a patent case, the merits of the contention of the Federal government and various *amici curiae* that genetic engineering presented "grave risks" of "pollution and disease, ...loss of genetic diversity, and...depreciat[ion of] the value of human life." The Court found that deciding whether the research "may pose a serious threat to the human race" or that such concerns were "fantasies generated by fear of the unknown" was a matter for Congress and the Executive.

> The choice we are urged to make is a matter of high policy for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts cannot. That process involves the balancing of competing values and interests, which in our democratic system is the business of elected representatives.

Id. at 317. The Commission has tried to advance the process of "investigation, examination, and study" but the ultimate "balancing of competing values and interests" is for elected officials.

[6] These suggestions draw on the work of the Federal Interagency Committee on Recombinant DNA Research, which was created at the direction of President Ford in 1976. That Committee recommended the adoption of legislation explicitly to regulate recombinant DNA research, in light of the disjointed fashion in which existing legislation

One means of supplementing RAC, now that it is less active since the laboratory biohazards are no longer regarded as urgent matters, would be through a mixed public-private sector body established outside the Federal government.[7] This format has been employed in the initial work in other fields and there are plainly many organizations, ranging from those with academic and commercial interests to the religious bodies that prompted the present study, from which such a group could draw.

If it is felt that the extent of Federal responsibility is so great, both for safety and for promotion of this field, that a governmental body of greater breadth than the present RAC is needed, the Interagency Committee established in 1976, which has been inactive for the past several years, could be reinvigorated.[8] This would have the advantage of direct involvement of the leading Federal agencies but the disadvantage that its membership is entirely governmental and its meetings are not subject to the Federal Advisory Committees Act.

Rather than creating additions to RAC, it might be preferable to redesign it. The greater scope of work for the new RAC would have two aspects. First, the range of issues must certainly be broadened beyond laboratory and manufacturing hazards. Second, the involvement of other Federal bodies must be greater. Placing the successor to RAC outside of any one

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touched on the field. President Carter endorsed the resulting legislation, which was drafted by the Department of Health, Education and Welfare. It was introduced in Congress by Senator Edward M. Kennedy and Representative Paul G. Rogers. As redrafted by his health subcommittee after hearings, Senator Kennedy's bill called for the creation of an 11-member Presidential Commission (with 5 scientific and 6 lay members); the House version would have created a 15-person advisory committee to the Secretary of HEW.

[7] Corporate lawyer Milton Wessel has argued for the value, as a general matter, of institutions involved with science and technology pursuing a "rule of reason" in place of the adversary approach to the country's emerging socioscientific problems. If the private sector does not take the lead in resolving these emotion-laden issues in a fashion that serves the public interest, he believes the public will demand much greater direct governmental control. Milton R. Wessel, SCIENCE AND CONSCIENCE, Columbia Univ. Press, New York (1980).

[8] Dr. Fredrickson, who approves of the location of RAC within NIH as the governmental body with clearest responsibilities in the field, has also praised the interagency group:

> In addition to maintaining a desirable amount of ecumenical spirit within the federal bureaucracy, [it] had the virtue of being there and ready for immediate convocation in the event one of the hypothetical hazards materialized and national resources needed to be mobilized and coordinated.

Supra note 4, at manuscript p. 9.

department should promote this end, without making it merely a group of Federal agency representatives.[9]

One format would be the creation of a Genetic Engineering Commission (GEC) of 11 to 15 members from outside the government that would meet regularly to deal solely with this field. This group could have a majority of nonscientists—members of the general public as well as experts in ethics and philosophy, law, the social and behavioral sciences, and public and private management. In addition to a small staff, the GEC could have a series of Technical Panels that could provide expertise in (1) laboratory research, (2) agricultural and environmental uses and dangers, (3) manufacturing concerns, (4) human uses, and (5) international controls. It should also be able to draw on a panel of liaison officers from the Departments of Agriculture, Commerce, Defense, Energy, Health and Human Services (one each from the Centers for Disease Control, the National Institutes of Health, the Food and Drug Administration, and the National Institute for Occupational Safety and Health), Interior, Labor (including one from the Occupational Safety and Health Administration), and State; the National Science Foundation: the National Endowment for the Humanities: and the Environmental Protection Agency.

An alternative format would be to assign responsibility for oversight of genetic engineering to the body that succeeds the President's Commission.[10] This arrangement could have some advantages. Principally, it would permit the continuing oversight of gene splicing to be integrated into the consideration given to the social, legal, and ethical implications of other important developments in the biomedical arena. Also, it would recognize that the flow of work for such a body is not always at an even pace, a group with a more diverse mandate such as the President's Commission, could turn its attention to other areas rather than wasting time when there are no gene splicing issues needing attention, while still being ready should such issues need prompt attention,

[9] The experience of the Federal Interagency Committee is instructive That committee was created as a result of Congressional pressure. It was very active during its first year, when it was responding to a mandate from the highest levels of the Executive Branch to review the nature and scope of recombinant DNA activities in the Federal and private sectors and to recommend appropriate responses in terms of guidelines, regulations, and/or legislation. Once this task was complete, the committee slowly slid into quiescence, not because DNA research no longer raised important issues, but because the member agencies (other than NIH) were not active in this field so the committee did not have much to "coordinate."

[10] A two-year extension of the Commission is proposed in pending legislation, S.2311, the *Biomedical Research, Training, and Medical Library Assistance Amendments of 1982.*

Giving the assignment to the present Commission's successor might have several disadvantages, however. First, it seems unlikely that there will be any paucity of items to consider, in addition to the work presently performed by RAC, the agenda of any new body would be augmented by the many issues that RAC has felt were beyond its mandate. Second, not all the issues are ones of "bioethics," and assigning the task to the President's Commission might narrow the range of issues to be considered. (For example, in the present study, the Commission did not feel it had a basis for making judgments on the issues of patents and trade secrets, although they are important questions for the future of genetic engineering.) Third, by focusing primarily on genetic engineering, a GEC would be better able to develop among its members and staff the necessary familiarity with all the major issues and the underlying science.

Whatever mechanism is adopted, from among these or others, the quality and diversity of the members appointed to such a body, as well as the processes through which it deliberates, will be central determinants of its success. Whether the body is given formal regulatory powers, or merely the authority to issue guidelines and give advice, its major impact will rest on its ability to educate and to persuade. It must set its sights high if it is to function as "an agency for the protection of the future."[11] To protect the future people must sometimes be willing to act with vision and spirit as well as with humility—and striking a balance between courage and prudence is never easy.

[11] Arthur Lubow, *Playing God with DNA*, 8 NEW TIMES 48, 64 (Jan. 7, 1977) (quoting Robert L. Sinsheimer).

Glossary

A

Amino acids - The building blocks of proteins. There are 20 common amino acids, they are joined together in a strictly ordered "string" that determines the character of each protein.

Anneal - The process by which the complementary base pairs in the strands of DNA combine.

Bacteriophage (or phage) - A virus that multiplies in bacteria. Bacteriophage lambda is commonly used as a vector in recombinant DNA experiments.

Biotechnology - The collection of industrial processes that involve the use of biological systems. For some of these industries, these processes involve the use of genetically engineered microorganisms.

Cell fusion - The fusing together of two or more cells to become a single cell.

Chromosomes - The threadlike components of a cell nucleus that are composed of DNA and protein. They contain most of the cell's DNA.

Classical genetics - The body of knowledge that deals with the laws of inheritence of genes such as determined by appropriate test matings. (*Compare* molecular genetics.)

Clone - A group of genetically identical cells or organisms asexually descended from a common ancestor. All cells in the clone have the same genetic material and are exact copies of the original.

Conjugation - The one-way transfer of DNA between bacteria in cellular contact.

Crossing-over - A normal genetic event that always occurs during the reduction division of germ cell formation, which involves the breakage and reunion of DNA molecules.

Cut - A break that occurs in both strands of a DNA molecule opposite one another.

Cytoplasm - The protoplasm of a cell, external to the cell's nuclear membrane.

Diploid - A cell with the usual number of chromosomes, in contrast to haploid.

DNA (deoxyribonucleic acid) - The genetic material found in all living organisms. Every inherited characteristic has its origin somewhere in the code of each individual's complement of DNA.

DNA vector - A vehicle for transferring DNA from one cell to another.

Embryo - The early developmental stage of an organism produced from a fertilized egg.

Escherichia coli (E. coli) - A bacterium that commonly inhabits the human intestine. It is an organism used in many microbiological experiments.

Endonuclease - An enzyme that nicks or cuts DNA molecules; unlike a exonuclease, it does not require a free end to act. (*See also* restriction enzyme.)

Enzyme - A functional protein that catalyzes a chemical reaction. Enzymes control the rate of metabolic processes in an organism.

Eukaryote - A higher, compartmentalized cell characterized by its extensive internal structure and the presence of a nucleus containing the DNA. All multicellular organisms are eukaryotic. The simpler cells, the prokaryotes, have much less compartmentalization and internal structure; bacteria are prokaryotes.

Exonuclease - An enzyme that removes bases sequentially from the ends of a linear DNA molecule.

Fermentation - The biochemical process of converting a raw material such as glucose into a product such as ethanol.

Gamete - A mature reproductive cell.

Gene - The hereditary unit, such as a segment of DNA coding for a specific protein.

Gene expression - The manifestation of the genetic material of an organism as specific traits.

Gene mapping - Determining the relative locations of different genes on a given chromosome.

Genetic code - The biochemical basis of heredity consisting of codons (base triplets along the DNA sequence) that determine the specific amino acid sequence in proteins and that are the same for all forms of life studied so far.

Genetic drift - Changes of gene frequency in small populations due to chance preservation or extinction of particular genes.

Germ cell - The sex cell (sperm or egg). It differs from other cells in that it contains only half the usual number of chromosomes. Male and female germ cells fuse during fertilization.

Germ plasm - The total genetic variability available to an organism, represented by the pool of germ cells or seed.

Hybridoma - A rapidly proliferating cell made by fusing a myeloma cell with another cell. (Myeloma is a cancer of plasma cells.)

Haploid - A cell with half of the usual number of chromosomes.

Hormones - The "messenger" molecules of the body that help coordinate the actions of various tissues, they produce a specific effect on the activity of cells remote from their point of origin.

In vitro - Outside the living organism and in an artificial environment.

In vivo - Within the living organism.

Messenger RNA - Ribonucleic acid molecules that transmit the genetic information from the nucleus to the cytoplasm, where they guide protein synthesis.

Molecular genetics - Deals with the study of the nature and biochemisty of the genetic material. Includes the technologies of genetic engineering that involve the directed manipulation of the genetic material itself.

Monoclonal antibodies - Antibodies derived from a single source or clone of cells that recognize only one kind of antigen.

Mutation - Any change that alters the sequence of bases along the DNA, changing the genetic material.

Nick - A break in one strand of a DNA molecule in which no bases are removed.

Nucleic acid - A polymer composed of DNA or RNA subunits.

Nucleotides - The fundamental units of nucleic acids. They consist of one of the four bases—adenine, guanine, cytosine, and thymine (uracil in the case of RNA)—and its attached sugar-phosphate group.

Phage - (*See* bacteriophage.)

Plasmid - Hereditary material that is not part of a chromosome. Plasmids are circular and self-replicating. Because they are generally small and relatively simple, they are used in recombinant DNA experiments as acceptors of foreign DNA.

Polymorphism - A gene or unexpressed DNA variant that occurs in a population with a frequency too great to be explained by mutation.

Protein - A linear polymer of amino acids, proteins are the products of gene expression and are the functional and structural components of cells.

Recombinant DNA - The hybrid DNA produced by joining pieces of DNA from different sources.

Restriction enyzme - An enzyme within a bacterium that recognizes and degrades DNA from foreign organisms, thereby preserving the genetic integrity of the bacterium. In recombinant DNA experiments, restriction enyzmes are used as tiny biological “scissors” to slice foreign DNA before it is recombined with a vector. These enzymes are also called restriction endonucleases.

RNA (ribonucleic acid) - In its three forms—messenger RNA, transfer RNA, and ribosomal RNA—it assists in translating the genetic message of DNA into the finished protein.

"Shotgun" method - A technique for obtaining the desired gene that involves chopping up the entire genetic complement of a cell using restriction enzymes, then attaching each DNA fragment to a vector and transferring it into a bacterium, and finally screening the bacteria to locate those producing the desired product.

Somatic-cell - One of the cells composing parts of the body (*e.g.*, tissues, organs) other than a germ cell.

Totipotency - Capability of a cell, prior to differentiation, to express all of its genetic material.

Transduction - The process by which foreign DNA becomes incorporated into the genetic complement of the host cell.

Transformation - The transfer of genetic information by DNA separated from the cell.

Vector - A transmission agent: a DNA vector is a self-replicating DNA molecule that transfers a piece of DNA from one host to another.

Virus - An infectious agent, that requires a host cell in order for it to replicate. It is composed of either RNA or DNA wrapped in a protein coat.

Zygote - A fertilized egg.

Letter from Three General Secretaries

B

June 20, 1980

We are rapidly moving into a new era of fundamental danger triggered by the rapid growth of genetic engineering. Albeit, there may be opportunity for doing good; the very term suggests the danger. Who shall determine how human good is best served when new life forms are being engineered? Who shall control genetic experimentation and its results which could have untold implications for human survival? Who will benefit and who will bear any adverse consequences, directly or indirectly?

These are not ordinary questions. These are moral, ethical, and religious questions. They deal with the fundamental nature of human life and the dignity and worth of the individual human being.

With the Supreme Court decision allowing patents on new forms of life—a purpose that could not have been imagined when patent laws were written—it is obvious that these laws must be reexamined. But the issue goes far beyond patents.

New life forms may have dramatic potential for improving human life, whether by curing diseases, correcting genetic deficiencies or swallowing oil slicks. They may also, however, have unforeseen ramifications, and at times the cure may be worse than the original problem. New chemicals that ultimately prove to be lethal may be tightly controlled or banned, but we may not be able to "recall" a new life form. For unlike DDT or DES—both of which were in wide use before their tragic side effects were discovered—life forms reproduce and grow on their own and thus would be infinitely harder to contain.

Control of such life forms by any individual or group poses a potential threat to all of humanity. History has shown us that there will always be those who believe it appropriate to

"correct" our mental and social structures by genetic means, so as to fit their vision of humanity. This becomes more dangerous when the basic tools to do so are finally at hand. Those who would play God will be tempted as never before.

We also know from experience that it would be naive and unfair to ask private corporations to suddenly abandon the profit motive when it comes to genetic engineering. Private corporations develop and sell new products to make money, whether those products are automobiles or new forms of life. Yet when the products are new life forms, with all the risks entailed, shouldn't there be broader criteria than profit for determining their use and distribution? Given all the responsibility to God and to our fellow human beings, do we have the right to let experimentation and ownership of new life forms move ahead without public regulation?

These issues must be explored, and they must be explored now. It is not enough for the commercial, scientific or medical communities alone to examine them, they must be examined by individuals and groups who represent the broader public interest. In the long-term interest of all humanity, our government must launch a thorough examination of the entire spectrum of issues involved in genetic engineering to determine before it is too late what oversight and controls are necessary.

We believe, after careful investigation that no government agency or committee is currently exercising adequate oversight or control, nor addressing the fundamental ethical questions in a major way. Therefore, we intend to request that President Carter provide a way for representatives of a broad spectrum of our society to consider these matters and advise the government on its necessary role.

We also intend to ask the appropriate Congressional Committees to begin immediately a process of revising our patent laws looking to revisions that are necessary to deal with the new questions related to patenting life forms. In addition, we will ask our government to collaborate with other governments with the appropriate international bodies, such as the UN, to evolve international guidelines related to genetic engineering.

Finally, we pledge our own efforts to examine the religious and ethical issues involved in genetic engineering. The religious community must and will address these fundamental questions in a more urgent and organized way.

Dr. Claire Randall, General Secretary
National Council of Churches

Rabbi Bernard Mandelbaum, General Secretary
Synagogue Council of America

Bishop Thomas Kelly, General Secretary
United States Catholic Conference

Federal Government Involvement in Genetic Engineering*

C

Laboratory Research

Several agencies conduct or sponsor scientific research that either uses recombinant DNA molecules or studies the technique and its applications.

Department of Agriculture

The Department of Agriculture (USDA) funds several types of research involving genetic engineering in plants, animals, and microorganisms. Most research is in the following general categories: (1) studies of the normal genetic mechanisms of plants and animals (including the structure and function of nuclear, mitochondrial, and chloroplast genes, and the control of gene expression during development), with the goal of transferring functioning genes into higher organisms, (2) studies of viruses, bacteria, fungi, and other microbial agents that are pathogens or symbionts of plants, animals, or insects. The goal of the research is the eventual use of recognition sequences of microbes to introduce genes into higher organisms, extend the active range of nitrogen-fixing bacteria, or modify agents to achieve biological control of pathogenic microbes or insects, (3) studies to isolate and clone DNA sequences for useful proteins, and to gain the expression of these genes in bacteria in order to manufacture products, such as vaccines (*e.g.*, corn, soybean, wheat) and specific enzymes; and (4) studies to genetically engineer microbial organisms that will more efficiently produce useful fermentation products

* The information included in this Appendix was provided by government officials as part of a survey conducted by the President's Commission in September 1980 and updated in August 1982.

(*e.g.*, fermented foods, antibiotics) or degrade certain compounds (*e.g.*, industrial wastes, residual pesticides).

Department of Defense

The interest of the Department of Defense (DOD) and its subordinate military departments in the use of genetic engineering technology is principally directed to the prevention of disease and the fielding of those devices and methodologies that will ensure the survival and continued effectiveness of military personnel in a toxic environment.

Current DOD programs using genetic engineering techniques include vaccines for dysentery, malaria, botulism, anthrax, hemorrhagic fevers (including Rift Valley and Dengue fevers), rickettsial diseases, and trypanosomiases—all items of significance to the medical protection of U.S. Forces. Studies continue on cloning the human gene for acetylcholinesterase and the receptor for acetylcholine (which will be applied in developing treatments for military personnel exposed to chemical warfare agents) and on cloning the squid gene for Diisopropylfluorophosphatase for organophosphorus detoxification. Further studies deal with the molecular basis of marine biofouling.

Department of Energy

Many of the Department of Energy's (DOE) investigators have used recombinant DNA techniques in their work. Genes are being cloned in order to obtain sufficient material to analyze the structure of genes, to deduce structure-function relationships, to analyze the molecular basis of mutation, and to obtain genetic material as probes for analysis. The genes come from a variety of sources, but the cloning is always done in microorganisms.

Continuing studies of a number of proteins are being expanded to include analysis of the structure of the genes involved. These include trytophan synthetase, metallothionein, rhodopsin, globin, and several enzymes involved in DNA repair processes. Studies are also under way to look at several aspects of cancer, these include cloning the genes for several liver enzymes that are turned off when cancer develops, cloning a naturally occurring mouse tumor virus, and developing cloning and isolation techniques to search for genes that occur only in tumor tissues.

In other projects, a gene from *E. coli* is being put in Chinese hamster cells to study the occurrence of mutations, an unusual form of DNA is being prepared by recombinant DNA techniques to study how it is repaired, and genes in corn are being cloned to understand genetic elements called transposons. In a collaborative project with the Centers for Communi-

cable Diseases, fragments of DNA from a pathogenic organism are being cloned so probes can be developed to identify the organism in human tissues.

In projects related to biomass and fermentation, the genes for the multienzyme complex called cellulase are being cloned and analyzed, and an attempt is being made to introduce the enzyme xylose isomerase into certain kinds of yeast so they may ferment pentoses.

Future work being considered is along much the same line—examination of structure-function relationships of genes of particular interest, use of cloned genes to prepare hard-to-isolate gene products, and applied approaches as the needs and opportunities arise.

Environmental Protection Agency

The Office of Research and Development has undertaken a number of research studies and has represented the agency in various outside forums. Two assessments of the state of recombinant DNA usage in agricultural and industrial sectors and the impact of these applications on the environment have been commissioned. In addition, projects now in progress deal with events associated with environmental release of microbes. One study involves a computer simulation of the probability of escape of genomes from laboratories or commercial fermenters. Another is exploring survival of organisms in environmental media, and a third deals with the likelihood of genetical exchange of microbes in water and sewage. The office has participated with other groups and has established an institutional advisory group. Most recently, the staff initiated a seminar series designed to acquaint policymakers with environmental consequences of the technology, and they will participate in a research conference on the genetic control of environmental pollutants in 1983.

National Institutes of Health

The National Institutes of Health (NIH) is the major funder of basic research involving recombinant DNA techniques. It also supports several projects specifically designed for risk assessment. Both as a funding source and as part of its responsibilities for the protection of human research subjects, NIH will have a major role in clinical trials of gene therapy.

National Science Foundation

The National Science Foundation (NSF) funds several types of biological research involving recombinant DNA molecules: (1) gene regulation and expression, (2) structure and organization of chromosomes, (3) evolution and systematics, (4) organization and function of subcellular bodies, (5) transfer

of genes including nitrogen-fixing genes to plants, and (6) development of recombinant DNA technology.

Regulation

Several agencies have regulatory authority that extends to products of recombinant DNA technology.

Department of Agriculture

USDA has responsibilities for the inspection and certification of some products of recombinant DNA technology and the regulation of some organisms that may be used for recombinant DNA research. For example, USDA regulates importation into the United States of the foot-and-mouth virus that is used in vaccine research. Like other animal biological products, this vaccine would be licensed by the USDA.

USDA also establishes guidelines for the introduction and distribution of pathogenic microorganisms, other pests (insects, nematodes, noxious weeds), and plant germ plasm.

Environmental Protection Agency

In 1976, EPA's general counsel staff determined that some of the Federal statutes at EPA may apply to aspects of the bioengineering field. Their analysis included the Clean Air Act, Clean Water Act and Toxic Substances Control Act (TSCA) but did not address the other statutes under the Administrator.

Although several EPA statutes may apply, none has initiated a program to address biotechnology issues. Staff involved in administering the Federal Insecticide, Fungicide and Rodenticide Act and TSCA are currently reviewing the applied genetics field to consider the impact of the technology. The pesticide program has made the most progress, since it has already carried out registration reviews of over a dozen microbial agents that are used as pesticides. Generic testing guidelines are being readied for publication that will lay out the product chemistry, toxicology, environmental fate, and effects on nontarget species for testing for demonstration of safety in the registration process. The extent to which the guidelines may be altered to evaluate genetically engineered microbes as contrasted with naturally occurring agents has not been determined. Under TSCA, the Agency has broad authority over new and existing chemicals. The potential for TSCA to address the products of applied genetics as "new" chemicals is also being studied.

Federal Trade Commission

The Federal Trade Commission's (FTC) activities, which involve primarily enforcement actions, are concerned with the prevention and elimination of unfair business practices and restraint of trade. The Commission may exercise its enforcement powers to protect competition and consumers against practices that restrict research, development, production, or marketing of genetic technology and products or that might result in harm to consumers through unfair or deceptive advertising and marketing practices.

Department of Health and Human Services

Centers for Disease Control. The Centers for Disease Control (CDC) has responsibility for the interstate shipment of etiologic *(i.e.,* disease-inducing) agents and applies existing regulations (pertaining, for example, to volume and packaging) to DNA products identified as etiologic agents. *(See also* Department of Transportation below.) CDC provides a 24-hour hotline for reports of leakage of any such agents during transport.

Center for Infectious Diseases. As part of its responsibility for disease diagnosis and prevention, this Center conducts epidemiological investigations and research on a broad range of infectious diseases of public health importance. Considerable emphasis is placed on studying the molecular biology of many pathogenic microorganisms, their epidemiology, disease-producing mechanisms, antibiotic-resistance profile, and the development of candidate vaccines. Some of the molecular biology research involves the use of recombinant DNA technology. Examples of such research are: (1) cloning pencillinase-producing plasmid fragments from *Neisseria gonorrhoeae* in *E. Coli* to test for mobilization properties, and cloning *N. gonorrhoeae* genes for studies of proline synthesis and to further the use of auxotyping as an epidemiologic tool, (2) cloning genes for cadmium resistance and penicillinase production, which appear to be linked in *Staphylococcus aureus* and *S. epidermidis,* to determine if *S. epidermidis* can serve as a reservoir for the penicillinase genes, (3) cloning of genes from influenza viruses, poliovirus, rabiesvirus, and variola into bacteria to (a) study the structure and function of nucleic acids, (b) study viral pathogenesis, (c) develop molecular diagnostic procedures *(i.e.,* hybridization tests to identify viral agents), (d) improve and develop technology for use in molecular epidemiology, and (e) develop techniques for rapid sequencing of those peptides identified as the key antigenic moiety for influenza strains of known or anticipated epidemic potential, (4) cloning of Venezuelan equine encephalitis (VEE) virus genome into bacteria to enable subsequent reconstuctions of the viral genome se-

quence, to identify those regions that code for antigenic glycoproteins responsible for inducing immunity, and to reconstruct synthetically the amino acids required for a vaccine.

National Institutes for Occupational Safety and Health (NIOSH). NIOSH has recently undertaken a program to help identify potential health hazards to workers involved in recombinant DNA work. Walk-through surveys were conducted at six companies. Assessments of the potential for worker exposure were made based on process design and operations. NIOSH has also developed, with other CDC experts, guidelines for medical surveillance of exposed workers. Finally, NIOSH is continuing research into the best available fermentation control technology, which would form the basis for future control in the use of recombinant organisms.

Food and Drug Administration. Products under the Food and Drug Administration's (FDA) regulatory jurisdiction produced using recombinant DNA methods are subject to the same regulatory standards as products derived from conventional technologies.

In general, it is expected that new applications for FDA approval will be required for products obtained via recombiant DNA technology that fall under the Agency's regulatory purview. For the first such products, which are currently under clinical investigation, the requirement for new applications is clear: human insulin has not previously been marketed, recombinant human growth hormone (hGH) is actually methionyl-hGH, an analogue of the (approved) natural substance; and some recombinant human interferon preparations may be chemically different from the interferons derived directly from human cell sources.

Moreover, despite substantial experience with products such as vaccines, antibiotics, and toxoids derived from natural components of microorganisms, there is little experience with substances produced by genetic manipulation of microorganisms. Moreover, some of the microorganisms that may be employed to produce recombinant products have not been previously employed to produce drugs or biologics for human use. Thus, the possibility of encountering novel toxicities is a concern.

In the future, it is expected that, where consistent with individual Bureau policy, new applications will be required for products obtained via recombinant DNA technology, even if identity is demonstrated with the natural substance, or with a previously approved substance produced in a conventional way. However, each case will be handled on an ad hoc basis because of the many different kinds of products expected. Data required to support such applications will vary widely and depend on a number of factors, including, but not limited to: whether the product is identical to a previously approved

product; the projected length of time of use: the amount of previous experience with the product produced conventionally; and the amount of previous experience with recombinant DNA-derived substances.

National Institutes of Health. The National Institutes of Health (NIH), with its Recombinant DNA Advisory Committee, has established guidelines for the safe conduct of recombinant DNA research. The guidelines have been adopted by all Federal agencies and apply to all Federally funded research, with voluntary compliance by the private sector. As part of the voluntary compliance scheme, NIH reviews some private research. A limited number of recombinant DNA experiments must be reviewed and approved by NIH prior to initiation. Biosafety committees are required at institutions that conduct recombinant DNA research and that are registered with NIH.

Department of Labor

Occupational Safety and Health Administration. The Occupational Safety and Health Administration (OSHA) will continue to monitor activities in genetic engineering and collect information that might be used as a basis for a regulatory effort. OSHA has no immediate plans for regulatory activities in this area.

Department of Transportation

Etiologic agents are categorized as hazardous materials and are subject to DOT regulations issued under the Hazardous Materials Transportation Act (18 U.S.C. 1801 *et seq.).* These regulations are associated with CDC regulations and apply to the transport of recombinant DNA molecules that have been incorporated into any etiologic agent listed in the CDC regulations.

Information/Education

Department of Commerce

The National Bureau of Standards has not been involved thus far in any work involving recombinant DNA. It expects, however, to carry out some of its traditional roles, such as establishing equivalency of chemical products and developing test methods and reference standards for products developed by recombinant DNA methods. One example might be determining whether any feedstocks produced with recombinant DNA methods contain by-products not produced by traditional processes. The Bureau's focus is on physics, chemistry, and engineering.

Until the Supreme Court reached its decision on the patentability of living organisms in June 1980, the Patent and

Trademark Office (PTO) had deferred the processing of the more than 100 patent applications involving products of genetic engineering. The PTO has now taken some form of action on all these applications, applying the usual standards of patentability. Patent applications involving use of recombinant DNA techniques or related technology were being received at the estimated rate of 10-15 per month in mid-1982.

The Department of Commerce is also interested in the protection of trade secrets, should private companies come under Federal regulation.

Department of State

The Department of State's involvement in genetic engineering, recombinant DNA and related technology emanates from its broad mandate to pursue U.S. foreign policy objectives, and its specific statutory responsibility for coordinating U.S. scientific and technological collaboration with other nations. Foreign policy concerns of relevance to genetic engineering include: international trade and commerce, particularly elimination of existing or potential nontariff trade barriers and the protection of patent rights; national security aspects of technology transfer, and environmental health and safety.

Although the Department of State does not directly sponsor or carry out research or development in this field, it obtains and provides information on policies and programs of other nations to support the R&D efforts of U.S. public and private institutions. The Department also coordinates US. participation in a broadening array of international organizations active in genetic engineering in an effort to influence the character of these efforts and to maximize their benefits. Such organizations include the World Health Organization, the UN Environment Program, the Economic Commission for Europe, and the Organization for Economic Cooperation and Development (OECD), as well as international nongovernmental bodies such as the International Council of Scientific Unions (ICSU).

National Academy of Sciences

The National Academy of Sciences (NAS) has not undertaken any activities focusing on the ethics of human applications of genetic technology. However, it has sponsored a Workshop of Priorities in Biotechnology Research for International Development. In addition, on May 20, 1982, a meeting was held of an ad hoc Committee on New Separation Processes for Genetic Engineering and Chemical and Energy Industries. A major focus of this meeting was on applications of biotechnology to separation processes, *e.g.*, removal of toxic or valuable contaminants from liquid phases. The meeting was

convened by NAS's Commission on Engineering and Technical Systems.

National Institutes of Health

In 1976 the Federal Interagency Committee on Recombinant DNA Research was formed under NIH auspices. It had three responsibilities: (1) review the nature and scope of DNA activities in the Federal and private sector, (2) determine the feasibility of extending NIH guidelines to all sectors, and (3) recommend legislative or executive action concerning these guidelines. The group met until 1980 at which time an Industrial Practices Subcommittee was formed. The full Committee recommended that legislation be passed extending NIH's recombinant DNA guidelines to the private sector, but Congress failed to pass the measure. Neither the full Interagency Committee nor its Industrial Practices Subcommittee is currently active.

National Science Foundation

Law and Social Sciences Program. This program supports a research project entitled "New Regulatory Forms: Recombinant DNA Research," which is carried out by Anselm Strauss at the University of California, San Francisco. As changes in science and technology have raised questions directly related to broader social, economic, political, and ethical issues, new law has been developed, requiring new patterns of regulation. This project specifically addresses issues of the scope of regulation, the role for technical specialists, and the criteria and standards applied by regulatory agencies and courts in terms of the history of regulation of DNA research. The study focuses on the relationships among interested parties in the regulatory arena, with attention to who those participants are and the "social worlds" they represent (the occupational settings in which they operate) and how they represent them. Emphasis is given to the strategy and tactics of conflict and negotiation among those parties. A manuscript describing this study is expected to be completed in early 1983.

Ethics and Values in Science and Technology. The program on Ethics and Values in Science and Technology (EVIST) supports research that shows promise of contributing to professional and public understanding of the ethical and value implications of genetic engineering. The program has supported the work of Charles Weiner, at MIT, to develop a historical archive of public and professional controversies surrounding recombinant DNA research and development. In September 1981 the NSF also awarded a grant to Clifford Grobstein, at the University of California, San Diego, to conduct a technology assessment of potential human applications of recent advances in genetics. Monographs are in preparation describing studies

by Sheldon Krimsky at Tufts University on a social history of the recombinant DNA controversy and by a team of researchers headed by Diana Dutton at Stanford University concerning the roles of public participation in controversies surrounding medical innovations, including a discussion of recombinant DNA.

Office of Technology Assessment, U.S. Congress

The Office of Technology Assessment has undertaken three studies in the field of genetics:

(1) Impacts of Applied Genetics: Micro-organisms, Plants and Animals: This report, released in April 1981, describes current and potential applications of classic and molecular genetic technologies to produce substances in three major industrial sectors—pharmaceuticals, chemicals, and food. Three applications involving release of genetically altered organisms to the environment are discussed: mineral leaching and recovery, enhanced oil recovery, and pollution control. Current and potential applications to higher plants and animals are described. Other parts of the report address the problems of assessing the risk of genetic engineering, the regulation of the technology, the patenting of life forms, and various science/society issues raised by the new genetic techniques. Policy options for Congressional consideration are described as well as the pros, cons, and consequences associated with them.

(2) Genetic Screening and Cytogenetic Surveillance in the Workplace: This assessment examines the state of the art of genetic screening and cytogenetic surveillance as means of identifying individuals at high risk for particular chemicals in the workplace or environments where the entire workforce may be at risk. It examines legal issues raised by genetic testing in the workplace, applicable ethical principles, and economic considerations. A survey of genetic testing in the workplace was conducted as part of the study, which is due to be completed in the fall of 1982.

(3) A Comparative Assessment of the Commercial Development of Biotechnology: This assessment examines whether biotechnology (which includes recombinant DNA, cell fusion, fermentation, and enzyme technology) is developing in the United States in a way that will leave the nation in a competitive position with other nations in the years ahead, Besides describing the state of the art here and in other countries, major influences likely to affect future development of the industry are reviewed. These include government policies on research funding, patents, health and safety regulations, antitrust laws, and taxation as well as industrial-academic relationships and their influence on funding, research, manpower, training, and information flow. The study is due to be completed in the summer of 1983.

The Commission's Process

D

Commission Hearings

September 16, 1980
Techniques and Problems

Dr. Gilbert S. Omenn, Associate Director for Human Resources, Veterans, and Labor, Office of Management and Budget, Executive Office of the President

Richard Roblin, Ph.D., Cancer Biology Program, Frederick Cancer Research Center, Frederick, Maryland

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Federal Activity

Dr. William Gartland, Director, Office of Recombinant DNA Activities, National Institutes of Health

Michael Lambert, Professional Assistant, Technology Assessment and Risk Analysis, National Science Foundation

Joshua Menkes, Ph.D., Technology Assessment and Risk Analysis Group, National Science Foundation

Arthur Norberg, Ph.D., Program Manager, Ethics and Values in Science and Technology, National Science Foundation

Dr. Joseph Perpich, Executive Secretary, Federal Interagency Advisory Committee on Recombinant DNA Research, National Institutes of Health

Dr. Bernard Talbot, Executive Secretary, Industrial Practices Subcommittee, National Institutes of Health

July 10, 1982
Panel Discussion of Draft Report

Dr. French Anderson, Chief, Laboratory of Molecular Hematology, National Heart, Lung, and Blood Institute, National Institutes of Health

Nicholas Wade, Editorial Board, *New York Times* and author of *The Ultimate Experiment: Man-Made Evolution*

Public Comment

J. Robert Nelson, Ph.D., Professor of Theology, Boston University

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These members served on the Commission while this study was being conducted, their terms of service, which were completed before the Report was approved, are indicated in parentheses.

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Mathilde Krim (Nov. 1979-Dec. 1981)

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