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Regulating Human Gene Therapy

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REGULATING HUMAN GENE THERAPY†

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I. SETTING THE STAGE

The question became whether A-T and G-C base pairs would easily fit the backbone configuration devised during the previous two weeks. At first glance this looked like a good bet, since I had left free in the center a large vacant area for the bases. However we both knew that we would not be home until a complete model was built in which all the stereochemical contacts were satisfactory. There was also the obvious fact that the implications of its existence were far too important to risk crying wolf. Thus I felt slightly queasy when at lunch Francis winged into the Eagle [a pub near the laboratory], to tell everyone within hearing distance that we had found the secret of life.¹

The “Francis” in question is Francis Crick, then a young scientist who had not yet even earned his Ph.D. The author of the excerpt is James Watson, then twenty-four. It is England, 1953, and Watson and Crick have just uncovered the structure of deoxyribonucleic acid (DNA)—thus inaugurating a new era in the history of science.

Watson’s boastful account of the events surrounding their achievement, *The Double Helix*, combines the excitement of a good mystery with enough competition to warm the heart of the most ardent capitalist. There is Linus Pauling, within weeks or days of making the discovery himself, in hot pursuit of the answer—and the Nobel Prize it would eventually bring to Watson and Crick for getting there first. But was the excitement justified? It is true that the structure that Watson and Crick had just decoded was related to life itself—but only to its physical structure. The larger meaning of life, however—or of their discovery—was not to be uncovered so easily.

† This Article is based on an address delivered at the 1985 Benedum Centennial Lecture, West Virginia University College of Law.

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¹ J. WATSON, *THE DOUBLE HELIX* 197 (1968).

Sir Isaac Newton once observed: If I have seen further it is by standing on the shoulders of giants.² The work of Watson and Crick similarly rested on the earlier achievements of many others. The path that led to the code for DNA began at least as far back as the mid-nineteenth century in the garden of Gregor Mendel, an obscure monk in Austria whose breeding experiments with sweet pea plants led him to postulate the existence of genes.³ In 1868, just three years after Mendel published his findings, Frederick Miescher identified DNA, which he termed "nuclein."⁴ The function of DNA was not really understood until after almost a century of work,⁵ capped by the report of Watson and Crick, which revealed the structure of DNA, thereby demonstrating how information could be transformed between generations.⁶

Each cell in the human body has a nucleus, where genetic material is stored. In essence, this material acts as a blueprint guiding the cell to perform its appropriate function. Each cell normally contains twenty-three pairs of chromosomes, for a total of forty-six, with half of each pair inherited from one parent.⁷ Watson and Crick determined that each chromosome is a double helix of DNA. Particular segments of the DNA strands are more commonly termed genes.⁸ Each cell contains all the genetic blue-prints for the whole person. It is able to perform its specialized functions because only a portion of the genetic material (5-10%) is active at any one time—telling it to be a liver cell or a muscle cell, etc.⁹

The pace of scientific development in this field has moved with ever increasing

² Letter to Robert Hooke, Feb. 5, 1675-76. For a delightful romp through the alleged historic origins of the phrase see G. MERTON, *ON THE SHOULDERS OF GIANTS: A SHANDEAN POSTSCRIPT* (1965). *Metalogicon* bk. III, ch. iv (1159).

³ CONGRESS OF THE UNITED STATES, OFFICE OF TECHNOLOGY ASSESSMENT, *IMPACTS OF APPLIED GENETICS* 30 (1981) [hereinafter cited as *OTA APPLIED GENETICS*].

⁴ M. ROGERS, *BIOHAZARD* 22 (1977).

⁵ In 1944, Avery, McLeod, and McCarty, researchers at Rockefeller Institute, demonstrated bacterial transformation. They found that mixing DNA from a deadly strain of pneumonia bacteria that was itself dead with a live but harmless form of bacteria was lethal when injected in rats. Resistance continued, however to the suggestion that DNA was the source of heredity. See M. ROGERS, *supra* note 4, at 36.

In 1952, Alfred Hershey and Martha Chase performed a "blender experiment" at Cold Spring Harbor, Long Island, in which they marked phages [masses of DNA encased in a shell] with radioactive isotopes, allowed them to infect bacteria, then spun the mixture in a blender. They found that the DNA of the phage was securely inside the bacteria, with only its protein case left behind. M. ROGERS, *supra* note 4, at 37.

⁶ *OTA APPLIED GENETICS*, *supra* note 3, at 34. In what has been termed "one of the most coy statements in the literature of science," Watson and Crick concluded their paper on their discovery, which was published in *Nature*, April, 1953, by saying, "It has not escaped our notice that the specific pairing we have postulated suggests a possible copying mechanism for genetic material." M. ROGERS, *supra* note 4, at 38.

⁷ PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH, *SPlicing LIFE* 26 (1982) [hereinafter cited as *SPlicing LIFE*]. Sex-cells (sperm and ova) or germ-line cells, as they are termed, normally contain only twenty-three chromosomes.

⁸ *OTA APPLIED GENETICS*, *supra* note 3, at ix.

⁹ *SPlicing LIFE*, *supra* note 7, at 29.

speed. It was almost a century from Mendel to Watson and Crick, but only seventeen years passed until the next scientific breakthrough—the discovery in 1970 of the first DNA-cleaving enzyme, termed a “restriction” enzyme.¹⁰ These enzymes, extracted from bacteria, cut a DNA molecule at specific sequences that occur here and there along the double helix. Thus they enable scientists to reduce a very long DNA molecule into a set of discrete fragments that can be recombined with each other or joined with DNA from another organism to make a hybrid molecule.¹¹

II. ACT 1: SAFETY ISSUES

In 1971, only one year after the discovery of restriction enzymes, Paul Berg announced plans to join DNA from the SV40 human virus with another virus, and to insert this recombined DNA (rDNA) into *E. coli* bacteria.¹² Cancer researcher Robert Pollack, on hearing of the Berg proposal, reported:

I had a fit. SV40 is a small animal tumor virus; in tissue cultures in the lab, SV40 also transforms individual human cells, making them look very like tumor cells. . . . And *E. coli* just naturally lives in people. [Those involved] seemed to see it as a neat academic exercise. And I said, of all stupid things, at least put it into a phage [virus] then, that doesn't grow in a bug that grows in your gut. Because what if the combination escapes from the lab; then you have [the human virus] replicating in step with the *E. coli* and a constant exposure of the cells in your gut to the DNA of SV40. Which is a route in for the virus that never occurs in nature . . . and therefore something you might not be prepared to fend off.¹³

Pollack called Paul Berg, who soon learned that his Stanford colleagues were also uneasy about the risks of rDNA. Discussion of the risks spread. At the same time, work with restriction enzymes made it possible for anyone with “a moderate level of microbiologic skill [to] perform potentially hazardous genetic manipulations that two years earlier had not even been imaginable.”¹⁴ By January, 1973, one hundred researchers met at the Asilomar Conference Center on California's Monterey peninsula to discuss the risks. By June, 1973, at the Gordon Conference in New Hampshire, a majority of those present voted to send a letter to Phillip Handler, president of the National Academy of Sciences. The letter, published in

¹⁰ *Id.* at 32.

¹¹ Weinberg, *The Molecules of Life*, 253 *SCI. AM.* 48, 50, 52 (1985).

¹² Swazy, Sorenson & Wong, *Risks and Benefits, Rights and Responsibilities: A History of the Recombinant DNA Research Controversy*, 51 *S. CAL. L. REV.* 1019, 1021 (1978) [hereinafter cited as *Risks and Benefits*].

At the time, genetic work has focused only on the simple bacterium *Escherichia coli* or *E. coli*, which can be “infected” with foreign DNA using a bacteriophage or “phage.” But once the focus moves to more complex mechanisms, a bacteriophage will not work to carry the DNA to the cell. Berg turned to SV40 because he believed that a tumor virus could be used to bring DNA into a mammalian cell. M. ROGERS, *supra* note 4, at 43.

¹³ *Risks and Benefits*, *supra* note 12, at 1021.

¹⁴ M. ROGERS, *supra* note 4, at 52.

Science in 1973, expressed concern about the risks of creating hybrid DNA molecules.¹⁵ In April 1974, ten individuals, including Paul Berg and James Watson, met at MIT and decided to ask for a temporary moratorium on further research.¹⁶ Their letter, also published in *Science*, stated in part:

- Some of the rDNA molecules could prove hazardous. [We propose] that until the potential hazards of such recombinant DNA molecules are better evaluated, or until adequate methods are developed for preventing their spread, scientists throughout the world join with members of this committee in voluntarily deferring [experiments that pose such risks].¹⁷

Think of it: the scientists were concerned enough about the possible risks to ask for a self-imposed moratorium—an act without precedent in the history of science.

III. ACT 2: INTRAGOVERNMENTAL BATTLES—THE FIGHT TO REGULATE

Congress immediately set about holding hearings, although no legislation emerged.¹⁸ The executive branch, by contrast, moved fairly quickly to regulate. The National Institutes of Health (NIH) in 1974, building on the discussions begun in the scientific community, established a Recombinant DNA Advisory Committee (RAC). The RAC, chaired by NIH's deputy director for science, initially was made up entirely of scientists; it functioned more as a "kitchen cabinet" for NIH Director Donald S. Frederickson then as a group of outside advisors.¹⁹

In 1975 a second Asilomar conference was held. One very important product of Asilomar II was the suggestion of participants that a new safety measure could and should be employed for some rDNA work. In their view, safety could be assured for some rDNA experimentation by using not only physical containment, a safety measure already widely used in microbiology laboratories, but also "biological containment" by which they meant limiting either the infectivity of the vector (the

¹⁵ Singer & Soll, *Guidelines for DNA Hybrid Molecules*, 181 *Sci.* 1114 (1973) (letter).

¹⁶ J. AREEN, P. KING, S. GOLDBERG & A. CAPRON, *LAW, SCIENCE, AND MEDICINE* 15 (1984) [hereinafter cited as J. AREEN].

¹⁷ 185 *Sci.* 303 (1974) (letter).

¹⁸ For a discussion of legislation passed in 1985 over a veto by President Reagan, see text at note 90 *infra*.

¹⁹ J. AREEN, *supra* note 16, at 46. The membership of RAC was enlarged and broadened in 1978 by HEW Secretary Califano. Mr. Califano later reported:

[W]e sparked [the scientists'] spirited resistance when we added a number of ethicists, clergy, lawyers and lay persons to the committee. Fredrickson, however, saw the move as enriching the advisory group and strengthening a potential consensus on DNA research. Eventually many of the scientists who originally opposed the action appreciated some of the benefits of broad public participation.

CALIFANO, *GOVERNING AMERICA: AN INSIDER'S REPORT FROM THE WHITE HOUSE AND THE CABINET* 203 (1981).

agent that transfers a piece of DNA from one host to another), or limiting its dissemination and survival in the environment. The idea of biological containment was soon to be adopted by the RAC.²⁰

At about the same time, new research suggesting that DNA recombinants occurred more frequently in nature than had previously been recognized put to rest some of the early fears of opening a genetic Pandora's box.²¹ The influence of these new developments was reflected in 1976 when Dr. Frederickson, with the advice and counsel of the RAC, issued "Guidelines for Research Involving Recombinant DNA Molecules."²² These regulations ran to thirty-two triple-column printed pages in the Federal Register. Revised periodically since, most recently in 1984, the guidelines establish the RAC of NIH as the primary point of regulatory oversight in the federal government. Although in theory the guidelines apply only to rDNA research that is conducted or sponsored by an institution that receives support for such research from NIH, in practice most private research protocols have been submitted to the RAC for clearance.²³

The first judicial test of these new guidelines was also the first time the third branch of government looked at rDNA. In *Mack v. Califano*,²⁴ a resident of Frederick, Maryland, sought a temporary restraining order to stop any rDNA experiments from being conducted at nearby Ft. Detrick. The district court denied the request, noting that the defendants were in full compliance with the NIH guidelines. The court added:

In the planned experiment a derivative of *E. coli* K-12, which has been specifically designed to "self-destruct," will be employed. *E. coli* K-12 is unable to colonize

²⁰ Guidelines for Research Involving Recombinant DNA Molecules, 41 Fed. Reg. 27,902 (1976), (revised 49 Fed. Reg. 46,266 (1984)) [hereinafter cited as rDNA Regulations].

²¹ RISKS AND BENEFITS, *supra* note 12, at 1070.

²² rDNA Regulations, *supra* note 20.

²³ A notable exception is the proposal by Advanced Genetic Sciences, Inc. to field test genetically modified bacteria intended to protect crops against frost damage. The experiment was recommended for approval by the RAC in June, 1984, but the director of NIH withheld his approval to avoid applying different standards to private companies as opposed to academic researchers. (A previous injunction prevented NIH from approving an almost identical experiment proposed by Stephen Landow at the University of California. See *infra* note 26 and accompanying text.) Advanced Genetic Sciences therefore withdrew its application for the RAC and submitted it to EPA. 316 NATURE 183 (1985). On November 15, 1985, EPA approved the experiment against the advice of Martin Alexander of Cornell University, the chairman of EPA's own Scientific advisory panel Wash. Post, Nov. 15, 1985 at A2, col. 5.

In the absence of federal legislation, New York and a number of locations have passed legislation making the NIH guidelines mandatory. These localities are Amherst, Massachusetts; Berkeley, California; Boston, Massachusetts; Cambridge, Massachusetts; Emeryville, California; Newton, Massachusetts; Princeton, New Jersey; Somerville, Massachusetts; and Waltham, Massachusetts.

Hearings on The Potential Environmental Consequences of Genetic Engineering, Subcommittee on the Toxic Substances and Environmental Oversight of the Senate Committee on Environment and Public Works, 98th Cong., 2d. Sess. 40 (Sept. 25, 1984) (statement by Bernard Talbot, Acting Director, National Institute of Allergy and Infectious Diseases of the National Institutes of Health).

²⁴ *Mack v. Califano*, 447 F. Supp. 668 (D.D.C. 1978).

in the human intestinal tract and causes no known human or animal disease. This K-12 host-vector system will not survive passage through the intestinal tract of animals and will "die" because of its dependency on chemicals not found in nature.

Defendants further point out that the complete experiment will be conducted in P4 physical containment laboratories which have been shown to contain microbes presenting a known and demonstrable hazard to man.²⁵

Biological as well as physical containment was now recognized in case law. At the same time, the court's decision implicitly gave strong support to the power of the RAC by demonstrating that compliance with the NIH guidelines would help to protect future rDNA experiments from legal challenge.

Seven years later, in *Foundation on Economic Trends v. Heckler*,²⁶ the United States Court of Appeals for the District of Columbia Circuit was also asked to stop an rDNA experiment, this time an experiment involving the deliberate release of genetically engineered organisms into the air. The experiment in question, to be conducted by Drs. Nicholas Panopoulos and Steven Lindow, two scientists at the University of California, Berkeley, was designed to test the possibility of increasing the frost resistance of certain crops by applying genetically altered bacteria.²⁷ The RAC had approved the experiment in question without objection.²⁸ The minutes of the RAC meeting revealed only one sentence on the issue of dispersion, however, and that came almost verbatim from the proposal:

Although some movement of bacteria toward sites near treatment locations by insect or aerial transport *is possible*, the numbers of viable cells transported has been shown to be very small; and these cells are subject to biological and physical processes limiting survival.²⁹

The court observed, "Remarkably . . . RAC completely failed to consider the possible environmental impact from dispersion of genetically altered bacteria, however small the number and however subject to procedures limiting survival."³⁰ The court therefore halted the experiment until an adequate environmental assessment was completed.

Factual differences in the two cases may explain the difference in outcome. Deliberate release clearly raises safety issues different from those presented by experimentation that is intended to be confined to a laboratory setting. In *Mack*, moreover, unlike *Foundation on Economic Trends*, an environmental impact state-

²⁵ *Id.* at 669.

²⁶ *Foundation on Economic Trends v. Heckler*, 756 F.2d 143 (D.C. Cir. 1985). A federal district court had enjoined the experiments on May 18, 1984 at the request of the plaintiffs. The Court of Appeals was viewing that decision.

²⁷ *Id.* at 152.

²⁸ *Id.* at 153. This vote occurred after the proposal was modified and resubmitted. At an earlier meeting, the RAC vote was seven in favor, five opposed and two abstentions. *Id.*

²⁹ *Id.*

³⁰ *Id.*

ment was completed prior to the court's decision. Nonetheless, the strong impression remains that the willingness of the judiciary to defer to the expertise of the RAC had somewhat diminished, at least in the absence of evidence that relevant risk factors were fully considered by the RAC.

IV. ACT 3: HUMAN SUBJECTS

Scientific developments once again have moved the public debate on genetic engineering to a new issue. The concern now is human gene therapy. Within the next year or so, it is probable that protocols will be submitted to NIH to test the use of genetic engineering techniques to treat patients suffering from genetic defects.³¹ It is also likely that the subjects of this first use of genetic engineering in humans will be children; in this instance, children suffering from presently incurable conditions caused by a deficiency in a single gene. The most likely gene to be used in the first experiments on human gene therapy is adenosine deaminase (ADA), the absence of which results in severe combined immunodeficiency disease in which children have a greatly weakened resistance to infection and cannot survive the usual childhood diseases.³²

A. HHS Regulations

The shift in scientific focus means that a separate set of federal regulatory standards are relevant—the regulations of the United States Department of Health and Human Services (HHS) that protect human subjects of research conducted in any institution receiving HHS funds.³³ Again, a brief review of the pertinent history is in order both to understand why this separate set of regulations came into being in the first place and to understand why they are now relevant.

1. Historical Foundations

For the most part, the federal government does not attempt to regulate the relationship between a physician and his or her patient. Requirements are imposed on drugs and medical devices before they can be marketed,³⁴ but as if to underscore

³¹ See Anderson, *Prospects for Human Gene Therapy*, 226 *SCIENCE* 401 (1984) [hereinafter cited as Anderson].

³² Interview with W. French Anderson, September 23, 1985. Other possible genes to be used in the first experiments are: hypoxanthine-guanine phosphoribosyl transferase (HPRT), the absence of which results in Lesch-Nyhan disease (a severe neurological disorder that includes uncontrolled self-mutilation); and purine nucleoside phosphorylase (PNP), the absence of which results in another form of severe immunodeficiency disease. Anderson, *Human Gene Therapy: Scientific and Ethical Considerations*, 10 *J. MED. & PHIL.* 276 (1985).

³³ 45 C.F.R. § 46 (1983).

³⁴ See generally 21 C.F.R. § 314 (1985).

the traditional deference shown to the medical profession, once the Food and Drug Administration has approved a drug for one purpose, federal law does not prohibit a licensed physician from prescribing that drug for another purpose.³⁵

The deference shown to the medical profession is in part a reflection of principles of federalism: licensure and discipline of physicians are by tradition a matter of state rather than federal responsibility. But even at the state level, relatively little intrusion on the doctor-patient relationship occurs.

How, then, can one explain the federal regulations designed to protect patients or other human beings who are the subject of medical experimentation? The answer lies in large part in the revelations at Nuremberg about the activities of the Third Reich. In *United States v. Karl Brandt*,³⁶ also known as "The Medical Case," twenty physicians, including Karl Brandt, Hitler's personal physician, were tried for crimes that the defendants claimed were committed in the name of medical or scientific research. The court, composed of three judges from the United States, determined that:

In every single instance appearing in the record, subjects were used who did not consent to the experiments, indeed, as to some of the experiments, it is not even contended by the defendants that the subjects occupied the status of volunteers. In no case was the experimental subject at liberty of his own free choice to withdraw from any experiment. In many cases experiments were performed by unqualified persons, were conducted at random for no adequate scientific reason, and under revolting physical conditions. All of the experiments were conducted with unnecessary suffering and injury and but very little, if any precautions were taken to protect or safeguard the human subjects from the possibility of injury, disability, or death.³⁷

Indeed, the revelations of Nuremberg were so shocking, the conduct revealed so inhumane, that one is tempted to dismiss them as an aberration best buried in the past. But other, more recent examples of documented abuses in medical experimentation make it impossible to dismiss Nuremberg so easily. Two in particular stand out. First, in 1966, Dr. Henry Beecher, the Henry Isaiah Dorr Professor of Research at Harvard University, published a study in the *New England Journal of Medicine*, in which he documented study after study that had been published in professional journals and that violated the very principles of ethical research enunciated at Nuremberg.³⁸

For instance, consider example eighteen in Beecher's study:

Melanoma [a cancerous tumor] was transplanted from a daughter to her volunteering and informed mother, "in the hope of gaining a little better understanding of cancer immunity and in the hope that the production of tumor antibodies

³⁵ 21 C.F.R. § 1306.03 (1985).

³⁶ *Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10* (1949), reprinted in part in J. AREEN, *supra* note 16, at 907.

³⁷ J. AREEN, *supra* note 16, at 926.

³⁸ Beecher, *Ethics and Clinical Research*, 274 N. ENG. J. MED. 1354 (1966).

might be helpful in the treatment of the cancer patient." Since the daughter died on the day after the transplantation of the tumor into her mother, the hope expressed seems to have been more theoretical than practical, and the daughter's condition was described as "terminal" at the time the mother volunteered to be a recipient. The primary implant was widely excised on the twenty-fourth day after it had been placed in the mother. She died from metastatic melanoma on the four hundred and fifty-first day after transplantation. The evidence that this patient died of diffuse melanoma that metastasized from a small piece of transplanted tumor was considered conclusive.³⁹

Second, in 1972, the national press broke the story of an experiment first begun by the United States Public Health Service in Tuskegee, Alabama, in 1932, to determine the natural course of untreated syphilis.⁴⁰ The subjects were 400 poor, black men who were never informed that they were subjects in an experiment—or even that they had syphilis. The "experiment" continued long after effective treatment was available. Indeed, the Public Health Service warned the Alabama Health Department not to treat the test subjects when they took a mobile VD unit into Tuskegee in the early 1940s.⁴¹ As late as 1969, officials of the Centers for Disease Control decided to let the "experiment" continue still further.⁴² It stopped only when the headlines appeared.

Nuremberg could no longer be classed as a single aberration. The fact that the victims of Tuskegee were members of a minority group only strengthened the parallel. The time had come to establish national standards for protecting human subjects of research. As with rDNA, when Congress failed to act, the task of designing the standards fell by default to the executive branch.⁴³

2. Role of IRB's

HHS, an executive agency, was responsible for developing regulations dealing with such matters. The heart of the HHS regulations is a new entity: the Institutional Review Board (IRB). The regulations provide that each IRB must have at least five members, who represent more than one profession and both genders.⁴⁴ One is to be a lawyer, ethicist, or member of the clergy, and at least one must come from outside the institution sponsoring the research.⁴⁵ Each institution is free to establish its own IRB so long as the listed constraints are honored.

³⁹ *Id.* at 1356.

⁴⁰ See generally, J. AREEN, *supra* note 16, at 937-50; J. JONES, *BAD BLOOD: THE TUSKEEGEE SYPHILIS EXPERIMENT* (1981).

⁴¹ Brandt, *Racism and Research: The Case of the Tuskegee Syphilis Study*, 8 HASTINGS CTR. REP. 21 (1978).

⁴² *Id.*

⁴³ There is some indication that NIH may have acted to pre-empt Congressional legislation. See J. AREEN, *supra* 16, at 959.

⁴⁴ 45 C.F.R. § 46.107 (1983).

⁴⁵ *Id.*

Although the selection process may at first smack of the fox guarding the chicken coop, my own experience as a member of an IRB has dispelled most of my initial skepticism. The very *process* of presenting a proposal protocol for research involving human subjects to a committee assembled for the sole purpose of avoiding undue risk or harm to those subjects has done more to raise the consciousness of both researchers and IRB members about these issues than I would have anticipated. An unexpected benefit I have also observed is that the scientific quality of some protocols has been improved through the same process of presentation, explanation, and discussion with a group involving other experienced scientists and physicians.⁴⁶

3. Problems in Application of HHS Regulations

The HHS regulations formally direct the IRB to approve protocols only if "risks to subjects are minimized . . . by using procedures which are consistent with sound research design and which do not unnecessarily expose the subject to risk" and if "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects."⁴⁷ Unfortunately, no guidance is given on how to apply these principles to experiments on the frontiers of science such as human gene therapy.

The difficulty of deciding whether to approve a proposed experiment involving human subjects is compounded when the proposed subjects are children. Reflecting the traditional concern our society has felt for children, separate regulations have been issued to govern such research.⁴⁸ In addition to meeting the requirements imposed on research involving adult human subjects, these separate regulations specify that no more than minimal risk may be imposed on child-subjects unless the research "holds out the prospect of direct benefit to the individual subjects."⁴⁹

⁴⁶ See generally Nat'l Comm'n for the Protection of Human Subjects, Institutional Review Boards: Report and Recommendations (1978).

⁴⁷ 45 C.F.R. § 46.111(a)(1) & (a)(2) (1983).

⁴⁸ 48 Fed. Reg. 9814 (1983).

⁴⁹ 45 C.F.R. § 46.405. There are two other sections of the regulations that may be relevant. Section 46.406 addresses research involving "greater than minimal risk," but only if the risk represents a "minor" increase over minimal risk. The section permits such research if it is "likely to yield generally able knowledge about the subject's disorder or condition." Section 46.407 applies to research not covered by other sections. Thus, it would apply to research involving greater than minimal risk where the risk may not be justified by the anticipated benefit to the subjects. Research covered by section 46.407 can proceed only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) [determines]

(1) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children....

Unfortunately, the regulations do not clarify how likely the prospect of direct benefit must be to meet the standard.

Consider the children presently suffering from severe combined immunodeficiency disease (SCID). One of the best known victims was David, the boy who lived for twelve years in a germ-free bubble at the Baylor College of Medicine in Houston. Because of the disease, David's immune system failed to develop, leaving him vulnerable to common and normally harmless bacteria or viruses.⁵⁰ The current treatment for the disease is a bone marrow transplant, but there are not enough compatible, bone marrow donors.⁵¹

Should we proceed to experiment with the use of genetic engineering techniques to treat these children? The answer will turn in large part on whether the experimental procedure appears likely to be both safer than and at least as effective as the best available conventional treatment, which in the case of SCID would be a bone marrow transplant. To try an experimental procedure that was less effective or just as effective but less safe than available therapies would be clearly unjustified.

The first protocols to be submitted for approval concerning SCID will probably propose treating the subjects by altering the genetic structure of their bone marrow cells to enable them to produce the missing enzyme.⁵² The protocols will likely propose removing some of the subject's own bone marrow, delivering the missing genetic material to the bone marrow cells by "infecting" them with a retrovirus⁵³ to which the missing DNA segment has been added, and then reimplanting the treated bone marrow in the subject.⁵⁴ Such a treatment proposal, while designed to minimize the risk to the subjects that would arise if all the cells in their bodies were infected with rDNA, does not eliminate the possibility of inadvertently producing cancer. Viruses deposit the transplanted gene randomly in the cell's chromosomes. If it lands in a control region for one of the approximately twenty oncogenes—genes that can turn a normal cell into a cancer cell—a tumor could result.⁵⁵

Another possible risk of this procedure is that the altered genetic material might in some way be transmitted to third parties. One way of understanding the possible dangers of using a retrovirus to transfer the genetic material is to consider AIDS (acquired immune deficiency syndrome). AIDS is also caused by a retrovirus, one

⁵⁰ Thompson, *Researchers Ready to Try Gene Therapy*, Wash. Post, Dec. 19, 1984, at D7, col. 3. See also text at note 32 *supra*. See generally E. Gelfand & H. Dosch, *Diagnosis and Classification of Severe combine Immunodeficiency Disease*, 19 BRITISH DEFECTS 65 (1983).

⁵¹ *Id.*

⁵² Anderson, *supra* note 31, at 401-02.

⁵³ A retrovirus, unlike almost every other organism such as viruses, bacteria, plants, animals, and humans, stores its genetic information in ribonucleic acid (RNA) rather than in its DNA. Thompson, *Like No Other Human Disease*, Wash. Post, Sept. 4, 1985, at Health 10, col. 1.

⁵⁴ Anderson, *supra* note 31, at 401-02.

⁵⁵ Thompson, *supra* note 53.

called human T-cell lymphotropic virus (HTLV-3). The AIDS virus can be transmitted from one person to another in some circumstances, particularly via blood transfusions or sexual contact.⁵⁶ Similarly, a subject infected with a retrovirus might be able to transmit the virus to others who might then suffer any adverse effects associated with the retrovirus.

One of the most difficult aspects of assessing the immediate risks and benefits of a human gene therapy protocol for the reviewing committees is likely to be deciding whether there are sufficient animal data to justify proceeding with human clinical trials. A very controversial part of this assessment will be weighing whether or not it is necessary to conduct studies in primates, or at least in large animals, which could delay human trials for several years.⁵⁷ On this issue, at least, scientists are likely to be able to present data based on other situations in which the issue was the appropriateness of moving from animal to human trials. On the issue of longer term risks, by contrast, it will be harder to find appropriate analogies.

The first experiments that deliberately expose humans to rDNA arguably pose two longer term risks. First there is the risk of damage to the future of offspring of treated patients. The protocols described above are intended to involve only somatic cells,⁵⁸ or body cells, and thus should not affect future offspring of the patients. But there remains the risk of unintended consequences. There is also little doubt that the information gained by conducting such experiments may increase

⁵⁶ See generally Curran, Morgan, Hardy, Jaffe, Darrow & Dowdle, *The Epidemiology of AIDS: Current Stakes and Future Prospects*, 229 *SCIENCE* 1352 (1985):

The first cases of AIDS were reported in mid-1981. . . . By 30 August 1985, 12,932 cases of AIDS had been reported to the Centers for Disease Control. . . . Over 6,480 (50 percent) persons were known to have died.

. . . In most cases of AIDS in the United States, the virus appears to have been transmitted through one of four routes: sexual contact, intravenous drug administration with contaminated needles, administration of blood and blood products, and passage of the virus from infected mothers to their newborns.

. . . A recent report, however, describes a nurse in England who developed confirmed HTLV-III/LAV [the retrovirus that causes AIDS] antibody following a needlestick injury and exposure to the blood of an AIDS patient.

⁵⁷ W. French Anderson has argued: "Studies in vivo with primates are needed. A protocol similar to the one planned for human application should be carried out in primates, not just mice, because the endogenous proviral sequences in primate, including human, DNA are different from those in mouse DNA." 226 *SCIENCE* 401, 407 (1984).

The initial points to consider posed the following question: "2.a (1)(e) Has a protocol similar to the one proposed for a clinical trial been carried out in non-human primates and with what results? Specifically, is there any evidence that the retroviral vector has recombined with any endogenous or other viral sequences in the animals." 50 Fed. Reg. 2943 (1985).

The revised version provides: 2.e.(1)(e) Has a protocol similar to the one proposed for a clinical trial been carried out in non-human primates *and/or other animals*? What were the results? (emphasis added). 50 Fed. Reg. 33,465 (1985). The document thus has moved to a more neutral position on the issue of primate testing.

⁵⁸ "Somatic cells" are cells of the body other than germ-line cells which are the sex cells, i.e. sperm and egg cells.

the possibility of developing techniques for altering germ line cells at some point in the future. That technological ability, once it exists, means that humans will have the capacity to alter their own genetic future—the power to remake man in his own image.

Second, single gene therapy inevitably takes us closer to the possibility of being able to alter human traits that are shaped by more than one gene. Treating severe combined immunodeficiency disease is one thing, but it would be quite another for parents to be able to choose the IQ or appearance of their unborn child. The distinction has been described by Dr. French Anderson as the difference between gene therapy and eugenic genetic engineering.⁵⁹

B. *Assessing the Risks*

Bruce Mazlisch, in *The Fourth Discontinuity*,⁶⁰ built on Freud's notion of the great thinkers of the past who "had outraged man's naive self-love." First in the line was Copernicus, who taught that the earth was not the center of the universe. Second was Darwin, who "robbed man of his peculiar privilege of having been specially created, and relegated him to a descent from the animal world." Freud placed himself third for endeavoring to prove that we are not master of our own house, but influenced by unconscious motivations. American psychologist Jerome Brunner later revised Freud's list to emphasize elimination of discontinuities; that is, the establishment of a belief in a continuum of nature. According to Brunner, the Greek physicist-philosophers of the sixth century B.C., rather than Copernicus, established the first continuity for they conceived of the common laws of matter. Darwin was second for creating the continuity between man and the animal kingdom, and Freud third for the "continuity of organic lawfulness." This view is that accidents in human affairs can be seen as the continuity of the primitive, infantile, and archaic with the civilized and evolved. Mazlisch argued that computers would eliminate the fourth discontinuity, between man and machine. Perhaps. But surely a major discontinuity is our sense of ourselves as having qualities that are not subject to human manipulation. Genetic engineering opens the possibility that qualities we have considered personal, if not unique—intelligence, beauty, physical stamina—may in the future be for sale on the open market.

There is a strong consensus that somatic cell therapy is not different from many other types of medical intervention (organ transplants, bone marrow injections, etc.).⁶¹ There is a danger, however, that this consensus will push us unwittingly down a slippery slope to germ line cell therapy or even to eugenic genetic engineering. In vitro fertilization, which has spread rapidly in the last several years, is only

⁵⁹ Anderson, *supra* note 31, at 23.

⁶⁰ Mazlisch, *The Fourth Discontinuity*, *TECH. & CULTURE*, (Jan. 1967), at 1.

⁶¹ See, e.g., CONGRESS OF THE UNITED STATES, OFFICE OF TECHNOLOGY ASSESSMENT, *HUMAN GENE THERAPY—A BACKGROUND PAPER* (1984); 50 Fed. Reg. 33,464 (1985).

the most recent in a long list of technologies that have altered our world without much public oversight.⁶² Although the possibility of moving closer to germ line or even eugenic genetic engineering should not by itself stop any somatic cell therapy, it does impose an obligation on all of us, I believe, to be aware of the risks of future abuse. We must also use the time we have now to determine the appropriate steps to take to control the risks that we will face once we have the technological capacity to perform germ-line or enhancement genetic engineering.

V. WHO SHOULD REGULATE?

Because so many important societal values must be weighed in deciding which, if any, of the first protocols for human gene therapy should be approved, it is obviously important to look closely at who will make the decision to approve or disapprove the protocols. In the United States, for the moment, at least three, and possibly four different committees are required to approve any protocol for human gene therapy performed with any public funds.

First, approval is needed from the IRB of the institution where the research will be conducted. Second, approval is needed from the Institutional Biosafety Committee (IBC), which is essentially a local RAC mandated by the rDNA guidelines.⁶³ Third, the RAC itself must approve the protocol.

Recognizing that it was not constituted with clinical studies in mind, the RAC in 1984 created a "Working Group on Human Gene Therapy," consisting of fifteen people, to advise it on these issues.⁶⁴ The Working Group includes four physicians, two microbiologists, three lawyers, three ethicists, two public policy experts, and one public member.⁶⁵ Four of the fifteen are also members of the RAC itself. Any human gene therapy protocol will now have to be reviewed by this fourth group as well. While the approval of the Working Group is not required as a matter of law, in practice it is unlikely that a rejection by it would be overturned by the full RAC.

Although the RAC should be commended for reaching out to broaden the base of available expertise in establishing the Working Group, unfortunately, the members of the Working Group were chosen without public consultation. Consequently, the RAC and the Working Group should proceed only after consulting as widely as possible with interested experts and lay groups alike.

For the moment, the Working Group has restricted itself to preparing for the arrival of the first protocols by issuing a set of "guidelines" to researchers. The guidelines outline information that the Working Group anticipates it will need to

⁶² And this spread has occurred despite a ban on federal funding.

⁶³ See *supra* note 22.

⁶⁴ 44 Fed. Reg. 17,844 (1984).

⁶⁵ 50 Fed. Reg. 2940 (1985).

make a recommendation to the RAC on whether to approve a particular protocol.⁶⁶ Although much of the information identified is needed anyway for the reviews by the local IRB and IBC, some requirements are new.

Researchers are directed, for example, to report any serious adverse effects directly to NIH. This requirement reflects the federal involvement any such experiment will acquire by virtue of the approval process described above.⁶⁷ A second new requirement is that researchers report what steps will be taken to protect the privacy of any patients and families involved in the gene therapy.⁶⁸ Protection of privacy has become a major concern in light of the enormous public attention paid to the patients and families in recent cases involving new therapies, such as the transplant of a baboon heart to Baby Fae and the artificial heart transplants.⁶⁹

Significantly, even this modest step in the direction of broadening the base of decision-makers on human gene therapy was almost killed by bureaucratic infighting this past summer. NIH was about to publish a revised version of the initial points, which had been prepared by the Working Group, when NIH Director James B. Wyngaarden was asked by the Commissioner of FDA, Frank Young, to delay publication of the revised document until a Biotechnology Science Board (BSB) comes into existence.⁷⁰

The BSB was the product of the Cabinet Council on Natural Resources and the Environment Working Group on Biotechnology.⁷¹ The Council consists of representatives of the Departments of Interior, State, Justice, Agriculture, Commerce, Energy, Health and Human Services, and Labor, the Environmental Protection Agency, the Council on Environmental Quality, the Council of Economic Advisors, the Office of Management and Budget, the Office of Policy Development, the Office of Science and Technology Policy, and the National Science Foundation.⁷² Formed in April of 1984, the Council is reviewing federal regulatory rules and procedures relating to biotechnology, including the RAC.⁷³

The BSB was proposed December 31, 1984. It appears to have been designed primarily as a way to resolve conflicts among the five agencies in the federal government that have jurisdiction over some aspects of genetic engineering: EPA, FDA, the Department of Agriculture (USDA), NIH, and the National Science Foundation (NSF).⁷⁴ As envisioned by the Council, each of the five agencies would form

⁶⁶ 50 Fed. Reg. 2940 (1985) (revised 50 Fed. Reg. 33,464 (1985)).

⁶⁷ *Id.*

⁶⁸ *Id.*

⁶⁹ See, e.g., Altman, *Learning from Baby Fae*, N.Y. Times, Nov. 18, 1984, at 1, col. 1; Russell, *Heart Implant Problems Stir Doubts*, Wash. Post, June 7, 1985, at A1, col. 4.

⁷⁰ Culliton, *New Biotech Review Board Planned*, 229 SCIENCE 736 (1985).

⁷¹ 49 Fed. Reg. 50,856 (1984).

⁷² See Talbot, *supra* note 23, at 41.

⁷³ *Id.*

⁷⁴ 49 Fed. Reg. 50,856 (1984).

a "scientific advisory committee" that would be composed "principally of members of the scientific community who possess demonstrated, recognized expertises [sic] in disciplines related to biotechnology."⁷⁵ The five committees would in turn report to the BSB, which would be chartered under the Department of Health and Human Services and would report to the Assistant Secretary for Health.⁷⁶

The initial proposal indicated that ten of the members of the BSB would be members of one of the five advisory committees.⁷⁷ Presumably, each would be a scientist. Yet the proposal, in addition to listing an number of scientific review tasks, identified one function of the BSB as "provid[ing] a forum for public concerns."⁷⁸ It appears it would have been a forum with few, if any, members from outside the scientific community.

By November, 1985, the White House retreated from its original proposal. There will be a coordinating panel called the Biotechnology Science Coordinating Committee (BSCC), but it will be a "consensus" body without authority to overturn the actions of constituent agencies.⁷⁹

For the time being, approval has been given to the Working Group of the RAC to proceed. The revised points to consider were published in the Federal Register on August 19, 1985.⁸⁰ But the internal fight over the composition of the reviewing bodies is clearly not over. In its September 13, 1985 submission of comments on the proposed points to consider, the FDA commented:

Since . . . most of the critical decisions on individual investigators' submissions are likely to be scientific and medical ones, we suggest reconsideration of the membership of the RAC Working Group on Human Gene Therapy . . . which currently includes a large proportion of attorneys, ethicists, and public policy specialists. Arguably, the Working Group should be supplemented with more members with expertise in molecular biology, pharmacology, medicinal chemistry, and medicine.⁸¹

⁷⁵ 49 Fed. Reg. 50,905 (1984).

⁷⁶ *Id.*

⁷⁷ *Id.*

⁷⁸ 49 Fed. Reg. 50,904 (1984).

⁷⁹ P. Hiltz, Panel Created to Coordinate Biotechnology, Wash. Post, Nov. 12, 1985, at A 6 col. 1. Reportedly, the change was prompted by industry pressure. *Id.*

⁸⁰ 50 Fed. Reg. 33,464 (1985).

⁸¹ Letter to Dr. William Gartland, Director, Office of Recombinant DNA Activities, NIAID, NIH, Bethesda, Md. 20205 (Sept. 13, 1985).

It is interesting to compare the criticism of the composition of the working group submitted by Jeremy Rifkin and the Foundation on Economic Trends:

A given proposal may raise value-laden social and ethical issues that require more than the application of technical or scientific disciplines by the working group as well as by those groups that propose specific studies. There may be need for qualified representatives of the social sciences, including theologians, ethicists, social philosophers, anthropologists, and economists, as well as micro-biologists and various medical experts as voting members of the working group. The existence of only one or two representatives of such other disciplines

VI. RECOMMENDATIONS

It will not be easy to decide what limits, if any, to place on the development of human gene therapy. At a minimum, we must remain vigilant about the dangers of false cures. The temptation to help the victims of SCID or even of Lesch-Nyhan disease, which currently has no available cure, is understandably strong. But surely it should not lead to premature efforts that are scientifically unsupportable. Consider the cautionary language of *United States v. Rutherford*,⁸² in which the Supreme Court confronted the claim that the Federal Food Drug and Cosmetic Act should not be applied to terminally ill patients who wished to try Laetrile:

To accept the proposition that the safety and efficacy standards of the act have no relevance for terminal patients is to deny the Commissioner's authority over all drugs, however toxic or ineffectual, for such individuals. If history is any guide, this new market would not be long overlooked. Since the turn of the century, resourceful entrepreneurs have advertised a wide variety of reportedly simple and painless cures for cancer, including liniments of turpentine, mustard oil, eggs and ammonia; peat moss; arrangements of colored floodlamps, pastes made from glycerin and limburger cheese; mineral tablets; and "Fountain of Youth" mixtures of spices, oil and suet. . . . [T]his historical experience does suggest why Congress could reasonably have determined to protect the terminally ill, not less than other patients, from the vast range of self-styled panaceas that inventive minds can devise.⁸³

The reaction of the scientific community to the one known abuse of the relevant guidelines is encouraging. In 1980, Dr. Martin Cline, Chief of Hematology and Oncology at UCLA, attempted gene therapy on two patients suffering from a hereditary blood disorder. NIH found that Cline had violated both scientific and ethical research standards for human subjects. His own research data revealed little scientific basis to believe his effort would succeed.⁸⁴ Worse, he failed to disclose to the IRB or to the patients that they would receive recombinant DNA material *despite* the fact that the IRB went to considerable length to verify that the procedure would *not* involve recombinant DNA. Ultimately, his resignation as Chief of Hematology and Oncology was accepted; NIH withdrew his current grants and required a report of this matter to accompany grant applications for the next five years.⁸⁵

As the Cline affair suggests, we should also guard against what Judge David Bazelon has termed the "republic of science."⁸⁶ The idea of nonscientists having

may not be sufficient to assure that the group will recognize the potential issues or resolve them satisfactorily.

Letter from Edward Lee Rodgers, Counsel for Foundation of Economic Trends and Jeremy Rifkin to Director, Office of Recombinant DNA Activities, NIH (Sept. 18, 1985).

⁸² *United States v. Rutherford*, 442 U.S. 544 (1979).

⁸³ *Id.* at 557-58.

⁸⁴ Williamson, *Gene Therapy*, 298 NATURE 416, 418 (1982).

⁸⁵ PRESIDENT'S COMMISSION, *Protecting Human Subjects*, (Appendix E) 177, 182-85 (1981).

⁸⁶ Bazelon, *Coping with Technology Through the Legal Process*, 62 CORNELL L. REV. 817 (1977).

anything to do with science is a relatively recent one. Scientists have at times likened their profession to an autonomous, self-governing republic. To qualify for citizenship, one's scientific credentials must be in order. Only scientists, according to this view, should have a voice in the way science is governed. But these are not the principles on which a democratic society rests. Tracy Sonnenborn, speaking at the first conference on Genetic Intervention in Man in 1965, posed the issue this way:

The human problems raised by these new possibilities . . . are problems of morals, ethics, religion and politics. They are problems of how knowledge and the power that knowledge confers can be used. They could be used for good or ill, for the enslavement or the liberation of man. How they will be used obviously will not be decided by scientists alone. Nor should this be decided alone by professional politicians or theologians or by philosophers or by moralists. It should be decided on an enlightened and broadly based public opinion.⁸⁷

To a large extent, money has altered the tradition. Since World War II, the federal government in this country has largely paid for broad areas of scientific research, including the Manhattan project, the space program, and biomedical research in general. With the influx of so many government dollars, some government supervision became inevitable. But as the spread of *in vitro* fertilization demonstrates, denial of federal support is not always an effective sanction, at least in the late stages of the development of a new technology.

The difficulties of designing effective public controls should not obscure the need for such controls. Just as we have learned not to leave war solely to the generals, scientists alone should not control human gene therapy. It no doubt will be difficult to achieve appropriate control of gene therapy, or of any technology of comparable power for that matter, as the continuing debate on nuclear weapons suggests. The last analogy may be particularly apt, it turns out, for both nuclear weapons and gene therapy raise at least the possibility of ending the human race as we know it.⁸⁸ That potential, in turn, underscores the need to establish suitable public controls.

The Working Group on Human Gene Therapy and the RAC are a good first effort. At least as long as they consult a broad group of both scientific and lay advisors, they are likely to be good bodies for reviewing the risks and benefits of

⁸⁷ IMPORTANT TECHNOLOGICAL TRENDS/BIO TECHNOLOGY, II PROCEEDINGS OF THE FOURTH CONVOCATION OF ENGINEERING ACADEMICS, IV-A RAPPAPORT 224, May 29 - June 1, 1983 (quoted in *Hearing on Biotechnology Regulation of the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce*, 98th Cong., 2d Sess., Dec. 11, 1984 (statement by Frank E. Young, Commissioner, Food and Drug Administration)).

⁸⁸ In 1974 in explaining why a moratorium had been proposed on DNA research, Nobel laureate David Baltimore commented:

[A]lthough our dilemma . . . may differ from that of the atomic scientists in many details . . . , we all grew up with a question of the correctness of using the atomic bomb as one of the great moral dilemmas of the second part of the twentieth century. . . . I think you can see . . . a direct line of thinking.

Risks and Benefits, *supra* note 13, at 1024.

particular research protocols involving somatic cell gene therapy. Assessment of the risks of germ cell therapy, or of enhancement genetic engineering, by contrast, is beyond the present charge or resources of the Working Group.

Legislation that establishes a permanent advisory body charged with reviewing longer term risks has now been passed by the Congress over a veto by President Reagan.⁸⁹ The new law establishes a Biomedical Ethics Board modeled on the Office of Technology Assessment. The Board is to have twelve members, six from the Senate and six from the House. The Board is directed to:

study and report to the Congress on a continuing basis on the ethical issues arising from the delivery of health care and biomedical and behavioral research, including the protection of human subjects of such research and developments in genetic engineering (including activities in recombinant DNA technology) which have implications for human genetic engineering.

To conduct the studies and to make the reports, the Board is to appoint a Biomedical Ethics Advisory Committee of fourteen members: four distinguished in biomedical or behavioral research, three distinguished in medicine or the provision of health care, five distinguished in ethics, theology, law, the natural sciences, the social sciences, health administration, government, and/or public affairs, and two citizens with an interest in biomedical ethics. Each member is to serve for a term of four years, with the terms staggered to establish continuity in membership.

The structure of a Board plus a Committee holds out much promise. The members of the Board are to represent both parties in equal numbers, and thus should provide more consistent political direction than if it were yet another Presidential commission. The Committee, in turn, will be able to draw upon the experience of two previous Presidential commissions⁹⁰ as well as the RAC using scientific and ethical experts and lay members to tackle in a public forum both ethical and policy problems posed by new technologies. Congress may at last have found a structure that brings to bear the expertise of the relevant scientific communities in an open, democratic setting with the resources to tackle the enormous ethical and political problems posed for our society by future developments in genetic engineering. Now it should also find the funds to bring the Board to life.

⁸⁹ The Health Research Extension Act, H.R. 2409, Cong. Rec. 515925 (Nov. 20, 1985).

⁹⁰ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in 1974 by Pub. L. No. 93-348, 88 Stat. 352. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research was established in 1978 by Pub. L. 95-622, later amended by Pub. L. 97-377 (1982).

The National Commission was composed of eleven members appointed for the life of the commission by the Secretary of Health, Education and Welfare.

The President's Commission was also made up of eleven members. They were presidential appointees appointed for two, three, or four years, and thus the membership could, and in fact, did change over time to reflect the change from Carter to Reagan.

