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Human Gene Therapy: Ethics and Public Policy*

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ABSTRACT

The first three human gene transfer/therapy clinical protocols are now underway after having been subjected to an extensive review process by the Recombinant DNA Advisory Committee (RAC) and its Human Gene Therapy Subcommittee. The "Points to Consider" document developed by the RAC established the framework for evaluating genetic intervention protocols. This review process is taking place in a broader social context. Public attitude surveys in this country have indicated a general lack of knowledge in the area of genetic engineering but an acceptance of somatic-cell gene therapy as treatment for disease. Internationally, numerous policy statements on human genetic intervention have been published, all of which support the moral legitimacy of somatic-cell gene therapy for the cure of disease. The debate over the ethical issues related to somatic-cell gene therapy has evolved over a ten-year-period. The time has now come to begin a formal public process for the ethical assessment of germ-line genetic intervention.

OVERVIEW SUMMARY

An extensive discussion of the ethical issues relating to somatic-cell gene therapy has been taking place for a number of years. A consensus now appears to exist that somatic-cell gene therapy for the treatment of serious disease is morally correct. Walters, from his position as a leading ethicist who has followed the field of gene therapy throughout its history, now proposes that a formal public discussion should begin on germ-line gene therapy.

INTRODUCTION

THREE IMPORTANT MILESTONES in the history of medicine were passed between May 1989 and January 1991. In those 20 months, teams of researchers at the National Institutes of Health (NIH) initiated one human gene transfer study and two human gene therapy protocols. These are the first such studies in human patients since 1980, and the first publicly reviewed and approved human trials ever.

My essay will focus first on the social and ethical questions raised by these three proposals and by the review process that was employed to evaluate them. Next, I will consider the broader social context of research on gene therapy, both in the United States and abroad. Finally, I will discuss possible future developments, especially genetic interventions that would affect future generations. In this connection, I will recommend that a formal public process for the ethical assessment of germ-line genetic intervention begin now.

THE ETHICAL EVALUATION OF GENE THERAPY IN THE UNITED STATES, 1969–1990

Public discussion of the ethics of human gene therapy goes back in this country at least to the 1969 American Association for the Advancement of Science (AAAS) meeting held in Boston in late December. In a symposium at that meeting Bernard Davis presented a paper entitled "Threat and Promise in Genetic Engineering." This paper was later published in *Science* with the

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title "Prospects for Genetic Intervention in Man" (Davis, 1970). At the same symposium, theological ethicist James Gustafson discussed "Genetic Engineering and the Normative View of the Human" (Gustafson, 1973). The public discussion continued through the 1970s, with periodic symposia and articles.

In 1980, two events sparked renewed interest in the ethics of human gene therapy. The first was a letter to then-President Carter from leaders of the Jewish, Catholic, and Protestant religious communities, expressing concern about the potentially deleterious consequences of genetic engineering (President's Commission, 1982). A few months later the *Los Angeles Times* broke the story of Dr. Martin Cline's unapproved attempts to perform gene therapy on two patients afflicted with β-thalassemia, one patient in Israel and the other in Italy. The two major results of these events were, first, a detailed study of ethical issues in human genetic intervention by the President's Commission on Bioethics (President's Commission, 1982), and, second, a congressional hearing on "Human Genetic Engineering" convened in November 1982 by then-House-member Albert Gore, Jr. (U.S. Congress, 1982).

From the *Splicing Life* report of the President's Commission and the congressional hearing of 1982 one can draw a straight line to the review process for gene therapy proposals currently in place in the United States. The mediating institution was the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health. By early 1983 the RAC had already functioned for almost 8 years as the national standard-setting and review body for laboratory research with recombinant DNA and for early efforts to use recombinant DNA methods for the manufacture of pharmaceuticals.

In April 1983, RAC Chairman Robert Mitchell, a California attorney, asked the committee whether it wished to study and respond to the *Splicing Life* report of the President's Commission. The committee's affirmative response led, first, to an expression of its willingness to review human gene therapy protocols and, second, to the creation of a mechanism for the conduct of such reviews. In the summer of 1984 an interdisciplinary subcommittee to the RAC was established for the initial review of gene therapy protocols. The subcommittee included laboratory scientists, clinicians, lawyers, and ethicists in approximately equal numbers. In late 1984 and early 1985, this subcommittee developed and published a document entitled "Points to Consider in the Design and Submission of Somatic-Cell Human Gene Therapy Protocols" (National Institutes of Health, 1985). (For a detailed chronology of events in the work of the RAC and the subcommittee from 1983 to the present, please see Appendix A.)

From the beginning, the "Points to Consider" document combined elements from two traditions of research review—the concern to protect the human subjects who participate in biomedical research and the concern to protect workers and the environment from the potential biohazards of recombinant DNA research (Areen and King, 1990; Juengst, 1990). The central core of the "Points to Consider" can be stated in terms of seven rather simple questions.

1. What is the disease to be treated? In other words, researchers are asked whether the disease to be treated is sufficiently serious to warrant the use of a novel and untried approach to therapy. Any proposal to enhance a human ability rather than to cure a disease would immediately be screened out by this first question.
2. What alternative therapies are available for the treatment of the disease? The presupposition of this question is that diseases for which no satisfactory therapy currently exists are, other factors being equal, better candidates for this new type of treatment than are diseases that can be effectively managed by other means.
3. Based on prior laboratory and clinical studies, how *safe* is treatment with gene therapy likely to be for the patient, for the patient's offspring, and for other people who come into contact with the patient? In this question one can clearly see the merger of the human-subjects and the biohazards traditions of research review.
4. Based on prior laboratory and clinical studies, how *effective* is treatment with gene therapy likely to be for the patient? This question may present a considerable challenge to researchers if no other animal species are naturally afflicted with a particular human disease.
5. Assuming that questions 1–4 have been answered satisfactorily, what procedures will be employed to ensure fairness in the selection of subjects? This question is of particular importance if large numbers of medically eligible patients wish to participate in a clinical trial of gene therapy.
6. Assuming that all prior questions have been satisfactorily answered, how will patients or their parents be properly informed about the proposed study, and how will their consent be elicited? This question is especially pertinent with new and relatively complex approaches to therapy.
7. Again assuming that all prior questions have been satisfactorily answered, what steps will be taken to protect the privacy of gene-therapy patient and the confidentiality of medical information about the course of their treatment? Here the subcommittee wished to prevent a recurrence of the circus-like atmosphere that has surrounded several instances of therapeutic innovation in the recent past.

The public review process designed in 1984 and 1985 was applied to an actual clinical protocol for the first time in 1988. The first protocol, a gene-transfer study proposed by Steven A. Rosenberg and associates at NIH, was initially submitted to a local review committee on June 10th (N2-TIL, 1990). Public review by the RAC and the Human Gene Therapy Subcommittee began in July 1988 and was completed, after unanticipated complications, in January of 1989. The second protocol and the first human gene therapy proposal, the adenosine deaminase (ADA) deficiency study of NIH researchers R. Michael Blaese, W. French Anderson, and associates, was initially submitted to a local review committee on February 23, 1990 (ADA, 1990); the public review process lasted from March 30 to July 31. An even shorter period of review was required for the third protocol and the second human gene therapy proposal, the tumor necrosis factor study put forward by Dr. Rosenberg and his NIH colleagues. This protocol was submitted for local review on April 23, 1990 (TNF/TIL, 1990), and the public review process was completed on July 30 and 31.

What are the advantages and disadvantages of the current framework for reviewing human gene therapy protocols in the United States? Other commentators may be in a better position to provide an objective, external evaluation. The following re-

marks are based on participation in the review process since 1983. The major advantages of the existing framework are that it is public and that it is based on a set of national standards that were initially developed in a year-long process, and then periodically revised. Both the general press and the scientific press have in fact devoted detailed attention to the first three clinical protocols; and interested members of the public have ample information about the diseases being studied or treated, the researchers involved, and the major issues raised in the review process. All things considered, the formal review procedures in place today are a vast improvement—for both researchers and the public—over the *ad hoc* arrangements that prevailed in 1980.

Yet the RAC and its Subcommittee on Human Gene Therapy are in some ways fragile institutions, and the current framework for review is in certain respects untidy. Neither the parent committee nor the subcommittee was created by the Congress. In fact, each was created in part to fill a vacuum and in part to forestall congressional action, after Asilomar and after the *Splicing Life* report. In the early 1980s the RAC agreed to take on the contentious issue of the deliberate release of recombinant DNA into the environment; the organisms to be released were ice-minus bacteria. As a reward for its efforts, the RAC, or rather the Secretary of Health and Human Services, was hit with a lawsuit and chided by the United States Court of Appeals for the D.C. Circuit for failing to fulfill all the requirements of the National Environmental Policy Act (Areen and King, 1990). In 1985, the RAC was almost supplanted by an interagency super-RAC and almost removed from involvement with human gene therapy in a jurisdictional dispute between NIH and a sister agency (Beardsley, 1985; Culliton, 1985).

The untidiness of the current framework for review stems largely from the fact that the RAC is a committee of NIH, the principal federal funding agency for biomedical research in the United States. Thus, the RAC is technically authorized to review only gene-therapy proposals originating in institutions that receive NIH funding for recombinant DNA research. As the early history of the Atomic Energy Commission demonstrated, it is inherently difficult for a single government body both to promote and to regulate a field of endeavor.

The untidiness of the RAC's dual role became even more apparent when the first gene transfer protocol and the first two gene therapy protocols presented to the RAC were designed by intramural scientists from NIH itself. Despite these institutional ambiguities, my experience as a participant in the review process is, first, that the NIH Director has encouraged the RAC to fulfill its role critically and independently and, second, that the reviews of the initial protocols have been performed in a professional manner by well qualified experts in biology, medicine, ethics, and law, as well as by articulate laypeople.

THE BROADER SOCIAL CONTEXT FOR HUMAN GENE THERAPY RESEARCH

The research protocols and the review process that I have described have both developed within a much broader national and international context. A major element of the national context is the attitude of the American people toward human gene therapy. Fortunately, the Office of Technology Assessment commissioned Louis Harris & Associates to survey public attitudes toward biotechnology in general and gene therapy in particular. The poll was conducted among a random sample of 1,273 U.S. adults between October 30 and November 17, 1986 (OTA, 1987). One important finding of the survey was that public knowledge of genetic issues is limited: 63% of respondents acknowledged that they had heard or read "almost nothing" or "relatively little" about genetic engineering (OTA, 1987). When asked a general question about the morality of genetically altering human cells, only 52% of respondents replied that such alterations were " not morally wrong"; another 6% of respondents were not sure (OTA, 1987). However, when the respondents were presented with specific gene therapy scenarios involving fatal diseases or nonfatal birth defects, between 77% and 84% either strongly approved or somewhat approved (OTA, 1987). Asked specifically about somatic *versus* germ-like correction of "a genetic defect that would cause usually fatal diseases," a surprising 62% approved of both modes of correction and another 14% approved of correcting "only the gene that would carry the disease to future generations" (OTA, 1973). A similar survey conducted in 1987 by Research & Forecasts, Incorporated, for the Danish firm Novo Industri A/S found that 75% of Americans who were knowledgeable about genetic engineering approve the prevention of genetic disease through altering sperm or egg cells (*Novo Report*, 1987). In the Harris survey for OTA, only 44% of respondents approved of scientists changing the makeup of human cells to improve the intelligence level or physical characteristics that children would inherit; a majority of respondents disapproved (OTA, 1983).

There is also an international context for the ethical and public-policy debate about human gene therapy. While we do not have survey data from most countries or organizations like the data just cited, numerous policy statements on human genetic intervention have been published, especially since 1980. In several years of research, I have been able to identify 20 such statements that have been formulated between 1980 and 1990 by legislative bodies, government agencies or committees, profesisonal organizations, or religious bodies. The sources of these statements include specific committees in Denmark, Sweden, and the German Federal Republic, a standing committee in Australia, the Parliamentary Assembly of the Council of Europe, the World Medical Association, the Catholic Church, and the World Council of Churches. Without exception, all 20 of these policy statements accept the moral legitimacy of somatic cell gene therapy for the cure of disease. Evaluations of germline genetic intervention for the cure or prevention of disease are mixed, with a majority of the policy statements opposing such intervention. None of the 20 statements support the enhancement of human capabilities by genetic means. (For a list of the 20 statements, please see Appendix B.)

I do not wish to argue that the morality of a practice can be determined by surveys of either policy statements or public opinion. However, a unanimous judgment on somatic cell gene therapy by thoughtful individuals and groups from multiple cultures and traditions at least *supports* the philosophical arguments in favor of the practice. American public opinion can be mistaken, as it has been in the past on questions of gender equality and racial discrimination. However, the moral sentiments of our fellow citizens can be one important source of

moral knowledge for philosophers and are clearly relevant to the policymaking process in democracies. Both policy statements by opinion leaders and the views of the general public form the broader context for the review and conduct of human gene therapy.

A FUTURE ISSUE: GERM-LINE GENETIC INTERVENTION

My remaining comments are put forward in a spirit of exploration. They do not represent the viewpoint of any organization. In particular, I am not speaking on behalf of the Human Gene Therapy Subcommittee to the NIH RAC.

The time is ripe for a detailed public discussion of the ethical issues surrounding germ-line genetic intervention in humans. There are several recent developments that make this discussion especially appropriate in the decade of the 1990s. The first is the gradually increasing use of preimplantation diagnosis as a clinical procedure in *in vitro* fertilization programs in this country and abroad. The list of conditions that can be tested for currently includes the trisomies, Duchenne's muscular dystrophy, α- and β-thalassemia, and sickle cell anemia (Buster and Carson, 1989; Abstracts, 1990; Handyside *et al.*, 1990; Monk, 1990; Verlinsky *et al.*, 1990); new conditions, including cystic fibrosis, will surely be added to this list in the future, expecially as the human genome project completes the first years of a projected 15 years of intensive international effort.

A second factor is that laboratory models for the genetic modification of nonhuman mammalian preimplantation embryos have been developed by numerous laboratories, using multiple methods for genetic alteration of the embryos (Hammer *et al.*, 1984; Stout *et al.*, 1985; Costantini *et al.*, 1986; Mason *et al.*, 1986; Soriano *et al.*, 1986; Hooper *et al.*, 1987; Readhead *et al.*, 1987; Connelly *et al.*, 1989; Gordon, 1989). Phenotypic alterations in the animals resulting from these embryos can readily be produced, and the transmission of specific genetic characteristics to the offspring of these transgenic animals is also possible, though less predictable.

Third, the taboo mentality that at times surrounded the discussion of germ-line genetic intervention in the early 1980s is gradually being replaced by a willingness to consider other possibilities, beyond somatic cell gene therapy, for alleviating or preventing human disease. Since 1983 several respected ethicists, including John Fletcher (Fletcher, 1983, 1985) and Eric Juengst (Fowler *et al.*, 1989), and clinicians, including W. French Anderson (Anderson, 1989) and Robert M. Cook-Deegan (Cook-Deegan, 1990), have ventured to examine germ-line intervention in a relatively neutral and objective manner. Even more surprising than this academic discussion is the Declaration of Inuyama, adopted by 102 participants from 24 countries at a July 1990 meeting of the Council of International Organizations of Medical Sciences (CIOMS, 1990) [see pages 123–129, this issue]. The pertinent section of the declaration, which has not been widely covered by the Western press, reads as follows:

> VI. The modification of human germ cells for therapeutic or preventive purposes would be technically much more difficult than that of somatic cells and is not at present in prospect. However, such therapy might be the only means of treating certain conditions, and therefore continued discussion of both its technical and its ethical aspects is essential. Before germ-cell therapy is undertaken, its safety must be very well established, for changes in germ cells would affect the descendants of patients (CIOMS, 1990).

Robert Cook-Deegan has suggested in a recent article that the issue of germ-line genetic intervention is likely to arise in a specific clinical context. He outlines two possible scenarios. In the first, a couple requests preimplantation diagnosis following *in vitro* fertilization but expresses a moral preference for gene therapy rather than discard if the diagnosis shows the early embryo to be affected with a genetic disease. In the second scenario, both members of a couple are homozygous for the same genetic disease, yet both wish to be the genetic parents of their children. Presumably all of their progeny would be affected unless gene therapy were undertaken at some stage of their offspring's development (Cook-Deegan, 1990). In both of these scenarios germ-like transmission could be a foreseeable but unintended side effect of a therapeutic procedure intended primarily to cure disease in an (embryonic) individual.

A more distant and less probable scenario would be the development of techniques for the genetic repair of sperm and egg cells before fertilization occurs. What I as a layperson envision is a method by which the locus of a genetic defect could be precisely targeted in a reproductive cell, the defective sequence removed, and a properly functioning sequence substituted for the defective sequence. (The analogy from the realm of word processing would be the use of the search-and-replace function.) This kind of genetic repair, if it is ever technically feasible, could again be undertaken in response to reasonable requests by patients, either homozygotes or heterozygotes, who want to reduce the probability of transmitting a genetic defect to their children and grandchildren.

There is precedent within the RAC and the Human Gene Therapy Subcommittee for such anticipatory discussion of future technological possibilities. In December 1985 the subcommittee heard presentations by two scientists on retroviral vectors and on laboratory research with transgenic mice. In January 1986 the RAC held a similar forum on retroviral vectors, bone marrow transplantation, and candidate diseases for treatment by gene therapy. Perhaps the time is ripe for similar forums, or even a sustained study process, regarding germ-line genetic intervention.

The broader precedent for the germ-line discussion I am recommending is, however, the international public discussion of somatic cell gene therapy that occurred in the years 1969 through 1988. When the first clinical gene transfer and gene therapy proposals were put forward in 1988 and 1990, there were surprises, to be sure. The target cells in the early protocols were lymphocytes, not bone marrow cells, and malignant melanoma was not on everyone's short list of candidate diseases. But the central ethical questions in somatic cell gene transfer and therapy were well understood by researchers, by politicians, by the press, and by the general public. In addition, a national public review process was in place to receive and review the first proposals in light of those questions. It is, in my view, not too early to intensify and broaden the discussion of

germ-line genetic intervention—even if the fruits of current research efforts become apparent only in the 21st century.

APPENDIX A: CHRONOLOGY OF MAJOR EVENTS, 1983–1991

Meetings Leading to the Formation of the Working Group on Human Gene Therapy

1983

April 11: RAC meeting; endorsed proposal to form a working group to respond to President's Commission report entitled *Splicing Life*

June 24: First meeting of working group; recommendation that RAC be prepared to deal with ethical and social issues in specific proposals to apply genetic technology to humans; also, recommendation that membership of RAC be modified to enable it to consider such issues

September 19: RAC accepted working group's proposals, asked for further discussion of guidelines and review procedures

December 13: Second (and final) meeting of working group; draft language for revision of NIH Guidelines for Research Involving Recombinant DNA Molecules proposed; interdisciplinary working group or subcommittee of RAC suggested as initial review group for human gene therapy proposals

1984

January 5: Working group proposal published in *Federal Register*

February 6: RAC accepted working group proposal

April 26: NIH Director accepted RAC recommendations

Summer: Working Group on Human Gene Therapy appointed; membership included four laboratory scientists, three clinicians, three ethicists, three lawyers, and two public policy experts

Meetings of the Working Group on Human Gene Therapy

1984

[September 26: subgroup meeting; drafting of an outline for a guidance document]

October 12 (initial plenary meeting): discussion of a thirteen-page draft entitled "Points to Consider in the Design and Submission of Human Gene Therapy Protocols"

[October 29: RAC meeting, report from Working Group]

November 16 (second meeting): discussion of 11-page composite draft entitled "Points to Consider in the Design and Submission of Somatic Cell Gene Therapy Protocols"

1985

[January 22: "Points to Consider" published in *Federal Register* for comment]

[March 15: subgroup met to consider issues raised in 15 letters commenting on *Federal Register* version of "Points to Consider"]

April 1 (third meeting): further refinement of the "Points to Consider" in the light of public comments

[May 3: RAC meeting, report from Working Group]

[August 19: revised version of "Points to Consider" published in *Federal Register*]

[September 6: planned fourth meeting canceled]

[September 20: subgroup met to consider issues raised in four letters commenting on second *Federal Register* version of "Points to Consider"]

[September 23: RAC meeting; "Points to Consider" accepted]

December 16 (fourth meeting): presentations by W. French Anderson (on retroviral vectors), George Scangos (on transgenic animals), and Samuel Ackerman (on the FDA process for regulating investigational new drugs); working group expressed its willingness to review preclinical data

Meetings of the Human Gene Therapy Subcommittee

1986

[January 27: RAC meeting; presentations by David Martin (on candidate diseases for treatment by gene therapy), Robertson Parkman (on allogeneic bone marrow transplantation), and A. Dusty Miller (on the use of retroviral vectors)]

[February 25: memorandum from Executive Secretary of RAC and Subcommittee to "interested parties" requesting submission of preclinical data]

[No spring meeting of Subcommittee]

[May 12: W. French Anderson resigned from Subcommittee because of his plans to submit a gene therapy protocol in the foreseeable future]

August 8 (fifth meeting): review and revision of "Points to Consider"; consideration of March 26, 1986, letter from Committee for Responsible Genetics (CRG) proposing that NIH Guidelines on recombinant DNA research be revised to exclude human gene therapy if it could alter germ line cells and unless the therapy is aimed solely at the relief of a "life threatening or severely disabling condition"; subcommittee drafting and approval of a letter rejecting the CRG request; acceptance of concept of producing a lay-language summary of the "Points to Consider"

[September 29: RAC meeting and acceptance of Subcommittee position on CRG letter]

1987

[January 9: Lay Summary Subgroup meeting]

April 24 (sixth meeting): "Human Gene Therapy: Preclinical Data Document" by W. French Anderson *et al.* received and initially discussed; comments on the lay-language summary draft, now called "General Information on Gene Therapy for Human Patients"

[No meeting in July 1987]

December 7 (seventh meeting): detailed review of "*Preclinical Data Document*" by Anderson *et al.*; further refinement of "Gene Therapy for Human Patients"

1988

[No meeting on April 11]
[June 10: human gene transfer protocol of Steven A. Rosenberg *et al.* formally submitted for local review]
July 29 (eighth meeting): decision to extend scope of subcommittee oversight to include human gene *transfer* protocols; initial review of human gene transfer protocol submitted by Steven A. Rosenberg *et al.*; decision to defer approval pending submission of additional requested data
[September 29: conference call by subcommittee members, decision to recommend further deferral of Rosenberg *et al.* human gene transfer protocol pending submission of the additional data requested]
[October 3: RAC meeting; approval of Rosenberg *et al.* human gene transfer protocol by majority vote]
[October 18: Letter by NIH Director Wyngaarden to RAC Chairman McGarrity stating that human gene transfer protocol of Rosenberg *et al.* should be resubmitted, with additional data, to the Subcommittee]
December 9 (ninth meeting): approval of human gene transfer protocol submitted by Rosenberg *et al.*; discussion of optimal mode of interaction between Subcommittee and RAC; approval of "General Information Document"; discussion and rejection of proposal from the Foundation on Economic Trends to establish a Human Eugenics Advisory Committee parallel to the RAC and its Subcommittee

1989

[January 30: RAC meeting; NIH Director reported on his approval of the human gene transfer protocol; Foundation on Economic Trends announced filing of lawsuit to prevent enrollment of patients in protocol, further advocated establishment of Human Eugenics Advisory Committee; RAC approval of "General Information Document"]
[No March meeting of Subcommittee]
[March 31: meeting of Points to Consider Subcommittee]
July 31 (tenth meeting): revision of "Points to Consider," especially in order to include formally human gene transfer as well as human gene therapy
[September 1: revised "Points to Consider" document published in the *Federal Register*]
[October 6: RAC meeting; revised "Points to Consider" approved, with minor revision in title]

1990

[February 5: RAC meeting; presentations by Drs. Rosenberg, Blaese, and Anderson on the progress of the human gene transfer protocol; presentation by former NIH Director Fredrickson on the future role of the RAC; according to Dr. Fredrickson, human gene therapy should be central to RAC's role]
[February 23: human gene therapy protocol of Drs. R. Michael Blaese and W. French Anderson and associates for ADA deficiency formally submitted for local review]
[March 1: revised "Points to Consider" and "Gene Therapy for Human Patients: Information for the General Public" published in the *Federal Register*]
March 30 (eleventh meeting): initial presentation of human gene therapy protocol for ADA deficiency by Drs. Blaese and Anderson; recommendation that limit on number of patients in human gene transfer protocol be lifted
[March 30: RAC meeting; further review of Blaese and Anderson protocol; criticism of Subcommittee procedures for reviewing clinical protocols; acceptance of Subcommittee recommendations re lifting limit on number of patients in approved protocol]
[April 23: human gene therapy protocol of Dr. Rosenberg and associates for use of tumor necrosis factor gene in treatment of malignant melanoma formally submitted for local review]
June 1 (twelfth meeting): approval of Blaese–Anderson human gene therapy protocol, contingent on submission of additional data on several points
July 30 (thirteenth meeting): approval of Blaese–Anderson human gene therapy protocol for the treatment of ADA deficiency and of Rosenberg *et al.* gene therapy protocol for treatment of malignant melanoma using marked TIL cells carrying the gene for tumor necrosis factor; deferral of human gene transfer protocol from St. Jude's Hospital
[July 31: RAC meeting; approval of two human gene therapy protocols]
[October 16: RAC meeting; discussion of regional meetings and of future protocols]
November 30 (fourteenth meeting): approval of human gene transfer protocol from the University of Pittsburgh using TIL cells and interleukin-4; approval of human gene transfer protocol from St. Jude's Hospital studying relapse in acute myelogenous leukemia; deferral of additional human gene transfer protocols from St. Jude's Hospital and the University of Wisconsin; letter from Alexander Capron about the scope of the Subcommittee's mandate

1991

[February 4: RAC meeting; approval of human gene transfer protocol from St. Jude's Hospital studying relapse in acute myelogenous leukemia; deferral of human gene transfer protocol from the University of Pittsburgh; further discussion of the future role of RAC]

APPENDIX B: POLICY STATEMENTS ON HUMAN GENE THERAPY—AN INTERNATIONAL CHRONOLOGY

1980

World Council of Churches, Conference on Faith, Science, and the Future, *Faith and Science in an Unjust World*

1982

Parliamentary Assembly, Council of Europe: Recommendation 934 (1982) on genetic engineering
World Council of Churches, Working Committee on Church and Society, *Manipulating Life*
United States, President's Commission for the Study of Ethical

Problems in Medicine and Biomedical Research, *Splicing Life* report

1983

Pope John Paul II, Address on "The Ethics of Genetic Manipulation" to the 35th General Assembly of the World Medical Association in Venice

1984

Denmark, Indenrigsministeriet (Ministry of the Interior) *Fremskridtets Pris (The Price of Progress)*

Sweden, Gen-Ethikkommittén (Genetic Ethics Committee), *Genetisk Integritet (Genetic Integrity)*

United States, Congress, Office of Technology Assessment, *Human Gene Therapy: Background Paper*

1985

United States, National Institutes of Health, Human Gene Therapy Subcommittee (formerly, Working Group on Human Gene Therapy), "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols"

Federal Republic of Germany, Justice Minister and Minister for Research and Technology, Working Group (the Benda Commission), *In-Vitro Fertilisation, Genomanalyse und Gentherapie (In Vitro Fertilization, Genome-Analysis, and Gene Therapy)*

1986

National Council of Churches, Governing Board, policy statement on "Genetic Science for Human Benefit"

1987

German Federal Republic, Tenth Bundestag, Enquete-Kommission (Committee of Inquiry), *Chancen und Risiken der Gentechnologie (Opportunities and Risks of Genetic Technology)*

World Medical Association, "Statement on Genetic Counseling and Genetic Engineering" (39th World Medical Assembly, Madrid)

Canada, Medical Research Council, *Guidelines on Research Involving Human Subjects*

Australia, National Health and Medical Research Council, Medical Research Ethics Committee, *Ethical Aspects of Research on Human Gene Therapy*

1988

European Medical Research Councils, "Gene Therapy in Man"

American Medical Association, Council on Ethical and Judicial Affairs, "Opinion on Gene Therapy and Surrogate Mothers" [Report E: (I-88); title provided]

1989

Canada, Medical Research Council, *Discussion Paper: Research on Gene Therapy in Humans: Background and Guidelines*

European Commission, Working Party, *Ethics of New Reproductive Technologies (The Glover Report)*

1990

Council for International Organizations of Medical Sciences (CIOMS), "Genetics, Ethics and Human Values: Human Genome Mapping, Genetic Screening and Gene Therapy (The Declaration of Inuyama)"

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