DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
MINUTES OF THE RECOMBINANT DNA ADVISORY COMMITTEE

March 30, 1990
TABLE OF CONTENTS

I. Call to Order and Introductory Remarks

II. Approval of the Minutes of the February 5, 1990, Meeting of the Recombinant DNA Advisory Committee

III. Proposed Amendment to Appendix D-XIII of the *NIH Guidelines*

IV. Proposed Addition to Appendix D of the *NIH Guidelines*

V. Other Business

VI. Adjournment

The Recombinant DNA Advisory Committee (RAC) was convened for its forty-third meeting at 1:15 p.m. on March 30, 1990, in Building 31C, Conference Room 6, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892.
Dr. Gerard J. McGarrity (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public. The following were present for all or part of the meeting:

Committee members:

Candida R. T. Acosta
Ronald M. Atlas
Michael Brewer
Donald C. Carner
James F. Childress
Don B. Clewell
Charles J. Epstein
Robert P. Erickson

Martin F. Gellert
William N. Kelley
Brian F. Mannix
Robert D. McCreery
R. Scott McIvor
Richard C. Mulligan
Barbara E. Murray
Robert F. Murray

Gerald L. Musgrave
Paul E. Neiman
Monica Riley
Jeffrey W. Roberts
Nelson A. Wivel
(Executive Secretary)

A committee roster is attached (Attachment).

Ad hoc consultant:

LeRoy Walters, Kennedy Institute of Ethics

Presenters:

W. French Anderson, National Institutes of Health
R. Michael Blaese, National Institutes of Health
Steven A. Rosenberg, National Institutes of Health

Liaison representative:

Daniel P. Jones, National Endowment for the Humanities

The RAC is advisory to the National Institutes of Health (NIH), and its recommendations should not be considered as final or accepted.
The Office of Recombinant DNA Activities should be consulted for NIH policy on specific issues.

Non-voting agency representatives:

Emily M. Gause, DHHS Alcohol, Drug Abuse & Mental Health Administration
Henry I. Miller, DHHS Food and Drug Administration
George P. Shibley, Department of Agriculture

National Institutes of Health staff:

Cindy Able, NCI
Kim Badenhop, NCI
Leon Baltrucki, NHLBI
Shelby Berger, NCI
Sheri Bernstein, NHLBI

Barrie J. Carter, NIDDK
Michelle Carter, CC
Theresa K. Chen, NHLBI
Larry Couture, NHLBI
Kenneth Culver, NCI
Evan G. DeRenzo, CC
David A. Dichek, NHLBI
Irene Eckstrand, NIGMS
William Eliason, NIMH
Neal Goldman, CBER
Jay Greenblatt, NCI
Steve Groft, OD
Mary Ann Hutchings, NCI
Christine Ireland, OD
Debbie Johnson, CC
Attan Kasid, NCI
Kristen Kiser, OD
Kim Leichtling, NCI
Clark K. Lum, DRG
David Koeplin, NCI
Brian Martin, NIMH
Richard Morgan, NHLBI
Jay Moskowitz, OD
Donald Ralbovsky, OD
Alan L. Sandler, OD
Diane Striar, NHLBI
Carolyn Tolstoshev, NLM
Nancy Treptow, NCI

Others:

Natalie Angier, New York Times
James Barrett, Genetic Therapy, Inc.
Virginia Baskerville, NIH Observer
Tim Beardsley, Scientific American
Matt Bianchi, Wooten High School
David Blue, BioWorld, Inc.
Alexander Capron, University of Southern California
Bruce A. Carter, Department of Agriculture
Shing Chang, Cetus Corporation
Yawen Chiang, Genetic Therapy, Inc.
Thomas Copmann, Pharmaceutical Manufacturers Association
Barbara Culliton, Science Magazine
Martin A. Eglitis, Genetic Therapy, Inc.
Laurie Garrett, Newsday
Diane Gershon, Nature Magazine
Alan R. Goldhammer, Industrial Biotechnology Association
Pete Gorner, Chicago Tribune
Laurinda Harman, George Washington University
Michael Hershfield, Duke University

Robert Jackson, Lederle Laboratories
Attila T. Kadar, Food and Drug Administration
Rachel King, Genetic Therapy, Inc.
Jim Lee, Wooten High School
Rachel E. Levinson, Office of Science and Technology Policy
Steven Litwin, Department of Veterans Affairs
Albert Lum, Wooten High School
Abbey S. Meyers, National Organization for Rare Diseases
A. Dusty Miller, Fred Hutchinson Cancer Research Center
Robert C. Moen, Genetic Therapy, Inc.
Dan Mumford, Wooten High School
Robert Overell, Targeted Genetics
Thomas D. Palella, University of Michigan Medical Center
Robertson Parkman, Childrens Hospital of Los Angeles
Erwin Peters, Holohan Group, LTD
Rex Rhein, Biotechnology Newswatch
Marvin Rogul, Maryland Biotechnology Institute
Joyce Rudick, Environmental Protection Agency
Michael G. Schechtman, Department of Agriculture
Harold M. Schmeck, New York Times
Terry Sharrer, Smithsonian Institution
David Siev, Department of Agriculture
Min-Kyung Song, Food and Drug Administration
Clarence E. Styron, Monsanto Company
Frank Tang, Department of Agriculture
Paul Tolstoshev, Genetic Therapy, Inc.
Rick Weiss, Science News
Lisa White, Blue Sheet
John R. Wood, Department of Agriculture
Doris Zallen, VA Polytechnic Institute & State University

I. CALL TO ORDER AND INTRODUCTORY REMARKS:

Dr. McGarrity, the Chair, called the meeting of the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) to order at 1:30 p.m., March 30, 1990. He thanked Dr. LeRoy Walters, Chairman of the Human Gene Therapy Subcommittee, for his efficient handling of the morning session. He said the meeting was called pursuant to a *Federal Register* notice which, being 30 or more days prior to today's date, met requirements of the *NIH Guidelines for Research Involving Recombinant DNA Molecules*. He stated that the meeting would remain open to the public for its entirety, and that he expected the meeting to conclude within one day.

Dr. McGarrity noted that a quorum was present. In order to have all agenda items heard and discussed within the limited time available, he pledged to keep the agenda moving while making every attempt not to limit debate.

Dr. McGarrity noted there would be some modification to the distributed agenda, based upon actions taken during the meeting of the Human Gene Therapy Subcommittee during the morning. He

reminded the committee that in recognizing persons for comments he would use the following order: primary and secondary reviewers on each item as set forth in the agenda; other members of RAC; *ad hoc* consultants to the RAC; NIH staff members; members of the public who had submitted written comments; and finally, other members of the public.

II. APPROVAL OF THE MINUTES OF THE FEBRUARY 5, 1990, MEETING OF THE RECOMBINANT DNA ADVISORY COMMITTEE:

Dr. McGarrity called upon Dr. B. Murray to present comments on the minutes of the February 5, 1990, meeting of the RAC.
Dr. Murray reported that she had read the minutes and felt they accurately reflected what transpired at the meeting and moved their acceptance. Mr.McCreery stated he also had reviewed the minutes and had found them to be comprehensive and seconded
Dr. B. Murray's motion.

Dr. McGarrity asked for further comments on the minutes. There being no further comments, Dr. Murray asked for a vote on the motion for approval of the minutes. The motion passed by 20 in favor 0 opposed, and no abstentions.

III. PROPOSED AMENDMENT TO APPENDIX D-XIII OF THE NIH GUIDELINES:

Dr. McGarrity stated this was a consideration of a change in the patient numbers for the Human Gene Transfer Clinical Protocol. He asked if Drs. Anderson, Blaese, or Rosenberg wished to make any preliminary comments. They declined. Dr. McGarrity then called upon Dr. Walters to report on the results of the subcommittee's morning deliberations.

Dr. Walters reported a motion was unanimously approved by the subcommittee to lift the cap on the number of patients that could be enrolled in the protocol.

Dr. McGarrity then asked for comments from Drs. Neiman and McIvor. Dr. Neiman said he felt there had been complete discussion and general agreement on the justification for adding additional patients to the protocol. Dr. McIvor agreed that an increased number of patients could enhance the validity of the protocol.

Dr. McGarrity asked for a motion to accept the recommendation of the subcommittee. Mr. Brewer so moved, and Dr. Epstein seconded the motion.

Dr. McGarrity asked for further discussion. Dr. Atlas asked if there would be any cap at all on the patient enrollment.
Dr. Walters explained that since the investigators had said it was unlikely that more than 50 patients could be enrolled in the protocol, the subcommittee had agreed it would be simpler to lift the cap entirely.

Dr. Anderson said the National Cancer Institute (NCI) Institutional Review Board (IRB) has placed a cap of 50 patients on the study. However, because of a more frequent meeting schedule, it would be possible to amend this on a monthly basis, if required.

Dr. Childress stated that the Institutional Biosafety Committee does regularly review this and would have the opportunity to stop the protocol at any point.

Dr. McGarrity asked for further comments. There being no further discussion, the Chair put the motion to a vote. The motion to accept the recommendation of the subcommittee passed by 20 in favor, 0 opposed, and no abstentions.

IV. PROPOSED ADDITION TO APPENDIX D OF THE NIH GUIDELINES:

Dr. McGarrity said this item had also been discussed at the Human Gene Therapy Subcommittee meeting and involved proposed additions regarding the adenosine deaminase (ADA) deficiency protocol.
Dr. McGarrity asked Dr. Wivel to present a synthesis of the morning's discussion.

Dr. Wivel said Dr. Parkman had made a clear statement of concerns with regard to the hypotheses and supporting data involving the protocol and called upon him to repeat his statement for the full RAC.

Dr. Parkman said there were two potential mechanisms for a positive outcome in the protocol. One is that the T cells into which the gene has been placed would function as an extra source of enzyme, with the possibility existing that an intracellular source of enzyme would be superior to an extracellular source. The second possibility is that these ADA gene-containing T cells would be able to function normally and would, therefore, mediate immunological function. The improvements seen would be more analogous to a bone marrow transplant with the ADA-gene in the stem cells, allowing the T cells to mature and become immunologically normal. The question was which hypothesis the investigators felt was relevant and what preliminary *in vivo* and *in vitro* data would support such an hypothesis.

Dr. Wivel then called upon Dr. Kelley to restate points which he had made in the subcommittee meeting relative to the half-life of the T lymphocytes to betransduced. Dr. Kelley said he felt an estimate of the half-life of the cells in circulation was a very important variable and that evidence of the length of such half-life was not contained in the proposal and accompanying documentation.

Dr. McGarrity called for comments from the investigators or from members of the RAC regarding the protocol. Dr. Epstein suggested that Dr. Walters repeat the summary which he gave in the morning session as he felt it was an excellent summary of the entire discussion.

Dr. Walters said the discussion had centered on five points:

1. The investigators should now address the questions and issues raised by the subcommittee during the morning discussion.

2. The protocol should be responsive to the major categories in the **Points to Consider for Protocols for the Transfer of Recombinant DNA into the Genome of Human Subjects** document and should be organized in that order.

3. There should be external review or consultation on the use of polyethylene glycol-adenosine deaminase (PEG-ADA) as an alternative therapy.

4. There will be primary and secondary reviewers who will prepare written comments in advance of the next meeting of the subcommittee.

5. The next meeting of the subcommittee will be moved forward to June 1, 1990.

Dr. McGarrity then called upon Drs. Anderson and Blaese for comments. Dr. Anderson requested that comments and questions submitted to them be as specific as possible. He said, due to the time constraints of the morning session, all members of the subcommittee did not have the opportunity to voice their concerns in a complete manner. Therefore, primary and secondary reviewers should be assigned quickly so a timely response could be made before the next meeting of the subcommittee and the RAC.

Dr. McGarrity said that while the discussion had been somewhat redundant due to the overlap in membership of the committees, he felt it was important to place the discussion on the record of the RAC. He then called for further comments on the protocol.

Dr. R. Murray asked if there were questions or concerns raised by other review groups at the NIH relative to this proposed protocol. Dr. Anderson said they had already dealt with numerous issues raised by the NIH IBC. Further, they had replied to concerns from the NCI IRB and were now in the process of responding to a second series of concerns. He noted they also met with the IRB of the National Heart, Lung, and Blood Institute and were still in the process of replying to their concerns. Dr. Anderson said the second mailing to the RAC for this meeting contained the responses to the major issues from those three groups.

Dr. Anderson said the next step was to formulate a response in terms of the *Points to Consider* including any additional experiments and a point-by-point response to each of the primary and secondary reviewers in time for the next meeting of the Human Gene Therapy Subcommittee.

Dr. Atlas expressed his concern that the focus may shift to the efficacy of the current PEG-ADA protocol, rather than the human gene therapy protocol. He also said he wanted to see a question and answer format in the material presented to the RAC. He further questioned whether patient numbers would be adequate to determine if the treatment was ethical and effective. Further, he added that since this was a proposed treatment for children, the potential long-term impact of such treatment should be carefully studied and considered.

Dr. McGarrity then called upon Dr. Hershfield. He said he wished to clarify the statement by Dr. Anderson that he had reviewed this protocol for the IRB. He said that while he had received such a request from the NCI IRB several weeks ago, he had not yet seen the protocol. He said that, due to erroneous press reports of the March meeting, he had been under the impression that PEG-ADA was not involved.

Dr. McGarrity then thanked all participants for their comments and said that this item would appear again on future agendas of the RAC.

V. OTHER BUSINESS:

Dr. McGarrity reminded the committee that several months ago they had voted to hold public meetings out in the community to solicit comments. He stressed the importance of having members of the RAC present at these out of town meetings. He then called upon Dr. Wivel to comment on these proposed meetings.

Dr. Wivel said that at present it was felt that the majority of the meetings would take place in September of 1990, with two meetings taking place on the West Coast, two on the East Coast, and

one at an, as yet undetermined, site in the Midwest. He said that there had been a change in the date for the October meeting of the RAC, which is now scheduled for Tuesday, October 16, instead of Monday the 15th, as Monday will be reserved for one of the East Coast regional meetings. He urged members of the RAC to arrive a day early to attend this regional meeting. He said, where possible, there would be scheduled speakers and written summaries of their remarks.

Dr. McGarrity underlined the significance of these meetings and urged all members of the committee to make an attempt to attend at least one, if not more, of the regional meetings.

Dr. McGarrity said that, based on the morning's meeting of the Human Gene Therapy Subcommittee, further discussion was in order on the timeliness of the overall review of applications. He then called upon Dr. Kelley to discuss procedural issues relative to meetings of the RAC and the Human Gene Therapy Subcommittee. Dr. Kelley said that because of the ever increasing use of the gene therapy approach, both the Human Gene Therapy Subcommittee and the RAC could anticipate reviewing an increasing number of these proposals in the coming years. Therefore, it seems imperative that an efficient mechanism needs to be in place to expeditiously handle such reviews.

Dr. Kelley said that proposals submitted to a scientific group must, by their nature, deal with the scientific questions first. He said a mechanism to establish scientific validity of such proposals was necessary. He said he supported the basic concept of a primary and secondary review. However, he said there were difficulties in conducting a complete scientific discussion before the press and in the presence of the investigators. He questioned whether local review as the only scientific review was acceptable, and he felt that some type of national review was needed.

Dr. McGarrity said that, at present, due to the requirements in the *NIH Guidelines*, any proposals involving human gene therapy must come before the full RAC, and the RAC has already made a policy that anything involving human gene therapy must first go before the Human Gene Therapy Subcommittee. He noted that since the RAC must meet in open session, a confidential scientific review of applications is difficult if not impossible. He agreed with Dr. Kelley's perception that not all local IBCs are equally competent for human gene therapy review.

Dr. Childress questioned why Dr. Kelley felt that scientific discussion before the public was inhibiting. Dr. Kelley said that having the investigators present can be equally inhibiting. The Committee members would be less likely to make candid observations in their presence. Dr. Kelley said he is a strong proponent of the public being intimately involved in the process, but that a good scientific discussion prior to the full committee discussion is important.

Dr. R. Murray said the study section model is based on a different premise than the RAC review of protocols. He said study section discussions are based on the quality of science and judgments concerning the success or failure of the proposal with the investigators not present to defend their proposal. He said that the RAC review allowed for an exchange of views between the investigators and the committee, which permits the public to hear a full discussion of differences of opinion.

Dr. Rosenberg said he believed the purpose of any regulatory group was to facilitate progress and expressed concern that the current procedures and those being proposed would impede the ability to maximize progress. He said he had gone through an extraordinary amount of review prior to ever appearing before the RAC. Dr. Rosenberg said that study section review is based upon the need to identify excellent proposals from a very wide assortment so that allocation of funds will go to the most worthy projects. This is not the case with the RAC. Based on current procedures, there would

be at least a five month delay before a protocol presented next month to the IBC would be approved by the RAC. He urged that since the RAC is going to be reviewing clinical protocols for the treatment of lethal diseases, a more rapid mechanism be established.

Dr. Blaese commented that only protocols being funded with Government monies are required to come before the RAC. He expressed concern that others who should participate in this public forum would not, due to the stringent requirements and the lack of timeliness and flexibility in approval.

Dr. Gellert suggested a procedure which would consist of a discussion among RAC members, to be followed by an uninterrupted response by the investigators, rather than the current back and forth, question and answer format. He felt that it was essential to work within the context of the RAC's charter, rather than to attempt to change the charter. Dr. Erickson agreed with this suggestion.

Dr. Epstein said that a schedule of submittals should be established and adhered to. He said that he had only received a copy of the protocol two weeks ago and a list of amendments to the protocol the morning of the meeting. He said he did not feel this allowed for ample time for an initial review. He suggested a clearly defined time be set for the receipt of proposals, followed by an initial review done by a limited number of committee members. These reviews could then be circulated to all members of the committee and simultaneously transmitted to the investigators. They would have a specific time period in which to respond. By the time that the Human Gene Therapy Committee meeting convened, all material would have been amply reviewed.

Dr. Kelley suggested an "executive session" to allow for detailed scientific review. Dr. McGarrity said this was a question which must be first cleared through the NIH Legal Counsel. Dr. Wivel questioned whether "executive session" would be equated with "closed session." Dr. Kelley restated his position that the presence of the investigators could inhibit discussion. If the scientific issues could be considered by a small group, this could lead to a more efficient handling of the protocols.

Dr. Childress agreed, but felt that Dr. Epstein's suggestion of having the investigators present, but not participating, would avoid the appearance of having a closed session. Dr. Mulligan said he had felt constraint in discussing highly scientific issues because they might not appear to be immediately relevant to other members of the committee and the public. He supported the idea of separating the highly scientific discussion from the general discussion.

Dr. Walters expressed strong support for the tradition of totally open meetings by the RAC. He said it was particularly important that gene therapy or gene transfer be openly discussed to avoid the possible perception that there was anything to hide.
Dr. Epstein questioned whether written discussion would not also be inhibiting. Dr. Mulligan said it would not be, and that a formalization of the process was indicated.

Dr. Epstein asked if the RAC could direct the Human Gene Therapy Subcommittee to proceed in such a fashion. Dr. Wivel said he believed that there was flexibility in the ways the protocol could be reviewed. The subcommittee is advisory to the RAC; therefore, the RAC can make suggestions and recommendations to the subcommittee.

Dr. Epstein then moved that:

"The Office of Recombinant DNA Activities (ORDA) be directed to set up a review schedule for the subcommittee, detailing the times for receipt of proposal, initial review of proposals, written

response, written reviews, and time for responses to those reviews, prior to the meeting of the Human Gene Therapy Subcommittee, so that at the time of the subcommittee meeting the scientific issues and responses can be discussed, and then the full issues discussed by the subcommittee and recommendations made to the RAC."

Dr. Anderson said that currently, information submitted to other committees was routinely forwarded to the Human Gene Therapy Subcommittee and that the receipt of such information would probably not fall within the suggested schedule. Therefore, this motion would cause additional delays.

Dr. Epstein suggested that such information be included in the final responses to review which would occur relatively near to the time of the subcommittee meeting.

Dr. Childress seconded the motion.

Mr. Brewer questioned whether all proposals would receive the same amount of prior scientific review. He expressed concern that some proposals might not go through the elaborate scientific scrutiny that this protocol has prior to arriving at the RAC.

Dr. Rosenberg replied that at the clinical level, this intensity of review does not occur for any other type of clinical protocol. When a proposal comes from the NIH to the RAC it has already undergone extensive scientific and budgetary review. Proposals from extramural sources have already received funding by passing a study section review. What was being suggested could potentially add an additional five or six months of review before approval. The subcommittee should be looking at the science only in relation to issues of safety and he reiterated his concern that basic changes in the time-frame required for approval be enacted.

Dr. R. Murray cautioned the committee that not all proposals come from NIH and that any scheduling must take into account all submitters. Mr. McCreery said he thought the review of the science was being adequately performed by both IBC and IRB review. He suggested that the RAC was not the forum to decide issues of a time-frame for review. He asked that the Director of NIH be advised of this discussion and that he, in consultation with ORDA staff, would be in a better position to set such schedules.

Dr. Miller agreed with Mr. McCreery that all such proposals already receive extensive scientific review and that further over-review would act as a disincentive to extramural clinical investigators interested in this field. He complimented
Drs. Blaese, Rosenberg and Anderson on their dedication and patience with the evolving review process.

Dr. Kelley said that while he was a strong supporter of gene therapy, he felt the science was not impeccable. In order for the field to progress rapidly, a proper review process must be in place. Dr. Mulligan said he agreed with the Epstein motion, and it would not be a cause of delay.

Mr. Carner agreed with Mr. McCreery's suggestion that the NIH Director and the Chairman of the RAC arrive at suggestions for any change in process. Dr. McGarrity underlined that RAC is advisory to the Director. Therefore, the Director would take into account the discussion and advice of the RAC. He asked for further comments directed to Dr. Epstein's motion.

Dr. Epstein said a schedule for submission and replies was necessary. Other issues as to how many times the committee should meet and what issues they should address were not relevant and

should realistically be addressed by the NIH Director.

Dr. Rosenberg endorsed the suggestion of a timetable for submissions. However, he cautioned that when dealing with protocols for life-threatening diseases it would be unconscionable to allow a five-six month delay in the approval process.

Dr. Anderson said the RAC, which meets only three times per year, should not expect to have the same requirements as IBCs, IRBs, or the Food and Drug Administration, which meet on a monthly basis.
Dr. Atlas suggested that tentative meetings be scheduled on a more regular basis that could be canceled in the event that protocols were not forthcoming. Mr. Brewer said requirements for *Federal Register* notice made this very difficult.

Dr. Mulligan called the question on the motion, and the Chair called for a vote on Dr. Epstein's motion. The motion was unanimously approved.

Dr. Kelley then proposed an amendment to the motion to incorporate changes in the method of review which include the following six points:

1. That the committee have a primary and secondary reviewer on each proposal;

2. That the presentation of the science and the rationale for the proposed experiment be presented by the primary reviewer with any additional comments provided by the secondary reviewer, as appropriate;

3. That the discussion occur among the members of the Human Gene Therapy Subcommittee without further input from others present;

4. That at the conclusion of that discussion, others in the room who wish to comment, or ask questions, or modify interpretation, have an opportunity to do so;

5. That the investigators who were present throughout this proceeding, as the public, would have an opportunity to address the issues specifically; and,

6. The final discussion be restricted to the members of the Human Gene Therapy Subcommittee, although others may be present.

Dr. Atlas questioned the appropriateness of the RAC as a forum for this motion, and he suggested the Human Gene Therapy Subcommittee was the proper forum. Dr.Wivel said the amount of direction given to the subcommittee by the RAC is not addressed specifically in the *NIH Guidelines* or in the RAC Charter, and that all such motions would go to the Office of the Director and be reviewed by the Director, ORDA, and legal counsel.

Dr. Erickson seconded Dr. Kelley's motion.

Dr. Childress voiced opposition to the motion, stating that many of the issues addressed had already been discussed. In fact, much of what was mentioned has already been adopted as policy by the subcommittee. Dr. Mulligan agreed with Dr. Childress and said he questioned the need to formalize this process.

Mr. Carner said he felt that the motion already passed would be of benefit to both investigators and the subcommittee, but that further formalization of process was too complicated to discuss in a short time-frame. Dr. Mannix agreed with Mr. Carner, adding that he felt it was important to leave certain flexibility in these issues for the Chair of the subcommittee.

Dr. Walters, Chair of the Human Gene Therapy Subcommittee, said the members of the subcommittee clearly understood the need for more structured schedule and review process. However, he questioned the need for a mandate from the parent committee on issues of subcommittee process.

Dr. Anderson said his understanding of the purpose of both the subcommittee and the RAC was that they were in place to engender public confidence that research was taking place in a scientifically and ethically appropriate manner and that there was no public health hazard in such research. He said he felt any presentations, therefore, should address the public and its concerns. Lengthy discussion of scientific merit by primary and secondary reviewers would not meet this aim.

Dr. Mulligan said this discussion was good evidence of the difficulties involved with committee discussion of process and questioned whether further time should be spent on these issues. Dr. Epstein agreed that formal rules were perhaps unnecessary and said he felt there was some disparity in purpose between serving as a forum for public information and reviewing scientific merit. He said he felt the current *NIH Guidelines* require a scientific review; however, it is complicated by the emotional issues involved in dealing with research to treat people dying from cancer.

Dr. R. Murray spoke against the rigid structure of the amendment. He said that because of the extremely technical nature of the subject, the scientific discussion should be kept separate from the other issues.

Mr. McCreery called the question, with a second by Mr. Carner. Dr. McGarrity noted that according to parliamentary procedure, a two-thirds majority was needed for calling the question.

Dr. McGarrity then called for a vote on the issue of calling the question. The vote was 13 in favor, 6 opposed, and one abstention. The motion failed by not meeting a two-thirds majority.

Dr. McGarrity then asked for further comments on the motion on the floor. Dr. B. Murray suggested amending the motion to make it advisory, rather than mandatory. Dr. Kelley agreed to amend his motion in that respect.

Dr. Childress agreed that the motion should not be in the form of a mandate. He suggested that the scientific review focus more specifically on what is indispensable for the public review and less on interesting science from a scientific standpoint.

Dr. Neiman said that the Human Gene Therapy Subcommittee had a high concentration of members with scientific and technical expertise. He felt the RAC had created the subcommittee to address the specific technical and scientific issues raised by human gene therapy.

Dr. McGarrity called for further comment on the motion. There being no response, Dr. Wivel restated the motion as follows:

"That the Human Gene Therapy Subcommittee be advised to adopt procedures of operation roughly

analogous to the parent committee, wherein primary and secondary reviewers would be selected for consideration of any given protocol."

There being no further discussion, the Chair put the motion to a vote, and it was passed by 15 in favor, 3 opposed, and 2 abstentions.

Dr. McGarrity thanked the committee for its discussion and noted that the timeliness of review would need further input from subcommittees, RAC,ORDA, investigators, and the Office of the Director. He asked for further comments on this or other mechanisms.

Mr. McCreery asked if the NIH Director could address this matter to assist the committee in expediting the approval procedure. Dr. Wivel said that as gene therapy protocols become more frequent, new procedures for handling their review will evolve. He asked the committee to consider the viability of meeting more than three times annually. If this were the case, the budget of the committee would have to be taken into consideration.

Mr. McCreery then moved:

"That the Secretary and the NIH Director develop a protocol that would address the issues that have been discussed in this meeting, and that they come forth with recommendations, or perhaps rules, to the committee for procedure in the future."

The motion was seconded by Mr. Carner.

Dr. Rosenberg asked if a proposal were approved at the June 1, 1990, meeting of the subcommittee, whether they would have to wait until the next scheduled meeting of the RAC, October, 16, 1990, before beginning work on such a protocol. Dr.McGarrity said this was the current time-frame for the RAC and Human Gene Therapy Subcommittee meetings. Dr. Rosenberg asked if it was reasonable to wait four and a half months from the time a protocol is approved by the subcommittee for the RAC to act on that proposal. Dr.McGarrity said he was not addressing its reasonableness, but merely the present time-frame. Dr. Rosenberg requested a rescheduling of the RAC meeting.

Dr. Wivel reminded the committee that*Federal Register* notice must be published 30 days prior to any such meeting of the RAC. Dr. Epstein asked how soon it would be possible to schedule the next meeting of the RAC. Dr. Wivel said the true lead time was 45 days, given the necessary clearances for publications appearing in the *Federal Register*.

Mr. Brewer requested that if more RAC meetings were to be scheduled, that three to five months lead time be given so members could adjust their schedules. He further requested that the Human Gene Therapy Subcommittee meetings be scheduled for the day preceding the full RAC meeting.

There being no further discussion, Dr. McGarrity put
Mr. McCreery's motion to a vote. The motion passed unanimously.

Mr. Carner suggested scheduling an additional RAC meeting to avoid the four and a half month interval between the meeting of the Human Gene Therapy Subcommittee and the next regularly scheduled RAC meeting. Dr. McGarrity said he was concerned over the logistics of where the meeting could be held. Dr. Wivel assured the committee thatORDA would find a method to accommodate the meeting.

VI. ADJOURNMENT

Dr. McGarrity then thanked all those in attendance for their participation in the meeting, and he felt the public had been well served by the discussion.

Dr. McGarrity then brought to the attention of the committee the recent death of Dr. Royston Clowes, a prior member of the RAC. Dr. Clewell made brief remarks noting Dr. Clowes' contributions to science. Dr. McGarrity then called for a moment of silence to honor the memory of Dr. Clowes.

Having concluded the agenda and there being no further business to be discussed, Dr. McGarrity adjourned the Committee at 3:22 p.m., on March 30, 1990.

Nelson A. Wivel, M.D.
Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and Attachment are accurate and complete.

Date: 7/31/90

Gerard J. McGarrity, Ph.D.
Chairman
Recombinant DNA Advisory Committee
National Institutes of Health