DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING
January 14, 1993

The Recombinant DNA Advisory Committee (RAC) was convened for its fifty-second meeting at 9:00 a.m. on January 14, 1993, at the National Institutes of Health, Building 1, Wilson Hall, 9000 Rockville Pike, Bethesda, Maryland 20892. Dr. LeRoy B. Walters (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:

Nancy L. Buc, Weil, Gotshal, and Manges
Alexander Capron, University of Southern California (Conference Phone)
Ira H. Carmen, University of Illinois
Gary A. Chase, Johns Hopkins University
Patricia A. DeLeon, University of Delaware
E. Peter Geiduschek, University of California, San Diego (Conference Phone)
Robert Haselkorn, The University of Chicago (Conference Phone)
Susan S. Hirano, University of Wisconsin
Donald J. Krogstad, Tulane University School of Public Health
Brigid G. Leventhal, Johns Hopkins Hospital
Abbey S. Meyers, National Organization for Rare Disorders
A. Dusty Miller, Fred Hutchinson Cancer Research Center (Conference Phone)
Robertson Parkman, Childrens Hospital of Los Angeles
Leonard E. Post, Parke-Davis Pharmaceutical Division
Moselio Schaechter, Tufts University School of Medicine (Conference Phone)

LeRoy B. Walters, Kennedy Institute of Ethics, Georgetown University
Doris T. Zallen, VA Polytechnic Institute & State University

Executive Secretary:

Nelson A. Wivel, National Institutes of Health

Nonvoting Agency Representatives/Liaison Representatives:

Henry I. Miller, Food and Drug Administration
Kathy Hudson, Office of the Assistant Secretary for Health
Daniel Jones, National Endowment for the Humanities

National Institutes of Health Staff:

Bobbi Bennett, OD
Frederick Bonkovsky, CC
Norman Braveman, NIDR
Samuel Broder, NCI
Diane Bronzert, NCI
Sarah Carr, OD
Bruce Chabner, NCI
Sandy Chamblee, OD
Phillip Chen, OD
Mary Chunko, OD
John Diggs, OD
Tom Flavin, OD
MaryEllen Franko, NCI
William Gartland, NIDR
Mary Groesch, OD
Bernadine Healy, OD
Christine Ireland, OD
Susan Jenks, NCI
Kris Kiser, OD
Robert Lanman, OD
Becky Lawson, OD
Lance Liotta, OD
Jack Mahoney, OD
Richard Morgan, NHLBI
Jay Moskowitz, OD
Joan Porter, OD
Al Sandler, OD
Joanna Schneider, OD
Janet Smith, OD
Frances Taylor, NINDS
Debra Wilson, OD

Others:

Paul Aebersold, Food and Drug Administration

French Anderson, University of Southern California
James Barrett, Genetic Therapy, Inc.
Liz Bowie, The Baltimore Sun
Ann Driscoll, Fox, Bennett & Turner
Michelle Durand, The French Embassy
Ted Duvall, Medical News Network
Jeffrey Fox, Science News and Biotechnology
Diane Gershon, Nature
Paul Goldberg, The Cancer Letter
Kurt Gunter, Food and Drug Administration
Husband of Dr. Royston's Patient
Connie Lew, General Public
Richard Kozaic, Science Magazine
Alex Kuta, Food and Drug Administration
Charles Marwick, American Medical Association Journal
Katharine Matthews, Foundation on Economic Trends
Gerard McGarrity, Genetic Therapy, Inc.
Dori Meinert, Copley News Service
Robert Moen, Genetic Therapy,Inc.
Robert Murray, Howard University
Richard Norling, ABC Primetime Live
John Parker, The Blue Sheet
Raj Puri, Food and Drug Administration
Joyce Reilly, ABC Primetime Live
William Robinson, The Center for Applied Research
Ivor Royston, San Diego Cancer Research Center
Tomiko Shimada, Ambience Awareness International, Inc.
Robert Sobol, San Diego Cancer Research Center
Jennifer Sutton, Association of American Medical Colleges
Larry Thompson, Medical News Network
Paul Tolstoshev, Genetic Therapy, Inc.
Rick Vernard, Associated Press
Sue Walters, Kennedy Institute
Julie Wakefield, U.S. Medicine
R. Michael Williams, Cancer Treatment Centers
Janet Woodcock, Food and Drug Administration
William Yates, ABC Primetime Live
Kathryn Zoon, Food and Drug Administration

Call to Order

Dr. Wivel, Executive Secretary of the Recombinant DNA Advisory Committee (RAC), welcomed the new Chair, Dr. Leroy Walters, Director of the Center for Bioethics, Kennedy Institute of Ethics, Georgetown University, Washington, D.C. Dr. Wivel noted that Dr. Walters was a member of the working group that designed the *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA into the Genome of Human Subjects (Points to Consider)* and served as Chair of the Human Gene Therapy Subcommittee (HGTS) throughout its existence.

Opening Remarks/Walters

Dr. Walters presented a brief historical background on recombinant DNA research and gene therapy. In 1973, Maxine Singer wrote a letter to Science entitled, Guidelines for DNA Hybrid Molecules. In 1974, Paul Berg and 10 fellow committee members from the National Research Council wrote a letter to Science entitled, Potential Hazards of Recombinant DNA. In 1975, there was a meeting in Asilomar to discuss the hazards associated with recombinant DNA; the RAC was established following the Asilomar meeting. In 1976, the first version of the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* was published. In 1982, the Presidents Commission for the Study of Ethical Problems in Medicine and Biomedical Behavioral Research published a report entitled, *Splicing Life*. In 1984, the RAC established the Working Group on Human Gene Therapy to discuss issues relevant to the review and approval of human gene therapy protocols. In 1985, the first version of the *Points to Consider* was published in the *Federal Register*. In 1988, the RAC and NIH Director approved the first human gene transfer protocol. In 1990, the RAC and NIH Director approved the first two human gene therapy protocols. In December 1992, the 34th through the 37th human gene transfer/therapy protocols were recommended for approval by the RAC to the NIH Director. Also in December 1992, the RAC confronted the issue of compassionate use of gene therapy for the first time.

Dr. Walters explained that the purpose of providing this historical review is to remind the RAC that revolutionary advances have been made possible by recombinant DNA techniques within the last 20 years. The RAC has a long tradition and distinguished history. The RAC has survived by adapting to new circumstances and demonstrating a willingness to change policies and adapt new procedures. Each of the events that have been described have occurred with vigorous debate. Although reasonable solutions were often met with great difficulty, research has proceeded in a socially responsible manner. He stated that it is his hope that, through a process of honest and respectful discussion and debate, difficult problems will continue to be resolved.

Remarks of the Director of NIH/Dr. Bernadine Healy

Dr. Healy explained that she requested this special session of the RAC to discuss the NIH approval of Dr. Royston's compassionate plea exemption request and to address the urgent need to establish guidelines for handling such requests in the future.

Dr. Healy presented a chronology of the events that led to her decision to approve Dr. Royston's request. In early October, Senator Tom Harkin asked that the NIH give timely consideration to individual compassionate plea requests for approval of gene therapy procedures for terminally ill patients. Such a step would be a temporary solution to this problem until an appropriate, permanent, legislative solution setting forth the clear authority and mechanism for handling these cases can be achieved next year. This request was made on behalf of a 51-year-old former constituent suffering from a life-threatening Stage IV glioblastoma that has been unresponsive to conventional treatments.

At the time NIH received Senator Harkin's letter, there was insufficient information to make a decision regarding this particular patient or the proposed treatment. This request was the first compassionate plea for gene therapy received at NIH, and the NIH has no experience or mechanism for addressing such pleas. It was imperative that the RAC consider this issue at the December 4, 1992, meeting. Accordingly, Dr. Royston was invited to attend the December 1992 meeting to provide further information. Dr. Healy stated that although the RAC had a lengthy discussion on this issue, a formal recommendation concerning either the specific patient or the generic issue of compassionate plea exemptions was not forthcoming. Subsequently, Dr. Royston has submitted a formal written request for compassionate plea exemption to the NIH, including a copy of his Food and Drug Administration (FDA) single patient Investigational New Drug (IND) application and protocol, which were already pending at the FDA and his Institutional Review Board (IRB).

Dr. Lance Liotta, Deputy Director for Intramural Research, NIH, reviewed Dr. Royston's materials with the assistance of several oncologists at the National Cancer Institute (NCI), the staff of the Office of Human Subjects Research, and Dr. Wivel, Director of the Office of Recombinant DNA Activities (ORDA).

Consistent with the RAC's discussion on December 4, 1992, a letter was sent to Dr. Royston on December 21, 1992, recommending that his patient should consider entry into Dr. Edward Oldfield's glioblastoma protocol. At this time, Dr. Liotta requested additional information regarding local approvals and the status of the patient. Within 24 hours of this recommendation, NIH was advised that the patient and her family declined to be considered for Dr. Oldfield's protocol, in part because of the requirement for additional surgery. Moreover, this patient has already undergone several craniotomies that have probably caused her to be ineligible for Dr. Oldfield's protocol. In contrast, Dr. Royston's protocol is minimally invasive, involving the peripheral subcutaneous injection of gene-modified cells.

On December 23, 1992, Dr. Liotta, Dr. Wivel, and Mr. Lanman (NIH's legal counsel) met with the staff of the Assistant Secretary for Health and representatives of the FDA. At that meeting, the FDA representatives announced that Dr. Royston's single patient IND for compassionate use of gene therapy would probably be granted. In light of this announcement, Mr. Lanman advised NIH that absent any mechanism for compassionate plea exemption in the NIH Guidelines, it is within the authority of the NIH Director to make a decision regarding this request, pending FDA approval.

On December 28, 1992, the FDA advised NIH in writing that Dr. Royston's IND request had been approved with the use of Dr. Bernd Gansbacher's vector, NAPAD/IL2. Dr. Gansbacher had previously received NIH and FDA approval for the use of this vector in melanoma and renal cell carcinoma trials. The FDA viewed Dr. Royston's protocol as an extension of Dr. Gansbacher's protocol. Dr. Healy stated that based on FDA approval and concurrence from Dr. Liotta, Mr. Lanman, and several NIH institute and division directors, she approved Dr. Royston's compassionate plea request. Subsequently, this action was endorsed unanimously by the NIH institute and center directors.

Dr. Healy stated that her decision was based on the grave condition of the patient, the failure of all other available therapies, and an estimated survival of less than two months. First and foremost, the decision was a compassionate response to the request of a dying patient. This action was taken only after the assurance that there was no significant risk to either the health of the patient or the public.

Dr. Healy reminded the RAC that this meeting was not held for the purpose of critiquing this action. Rather, the RAC should consider with some urgency the development of a process for considering compassionate plea requests for gene therapy in the future. During the December 1992 meeting, one element was missing from the RAC's discussion; namely, the element of concern for an individual patient and their family. The evolution of genetic research now imposes this element upon us. Given the serious plight of Dr. Royston's patient, the following two alternatives offered by the RAC were unacceptable: (1) inclusion of the patient in Dr. Oldfield's protocol, and (2) continued deliberations at the March 1-2, 1993, RAC meeting.

Dr. Healy stated that there are at least three deficiencies in the current system for dealing with this new frontier of human gene therapy. First, the specific issue of compassionate use exemption is not encompassed by the *NIH Guidelines*, which embrace only research involving the use of recombinant DNA. Therefore, the argument can be made that a non-research compassionate plea exemption for a single patient is outside the scope of the RAC mandate. Second, should the *NIH Guidelines* be amended such that non-research exemptions fall within the purview of the RAC? The letter of the NIH Guidelines might support the exclusion of such cases, but the spirit of the RAC mandate, to protect the public and

provide a process for public comment on recombinant DNA research, might argue otherwise. The *NIH Guidelines* states that, The *NIH Guidelines* cannot anticipate every possible situation. The Guidelines will never be complete or final, since all conceivable experiments involving recombinant DNA cannot be foreseen. Therefore, it is the responsibility of the institution and those associated with it to adhere to the intent of the Guidelines as well as to their specifics. This statement suggests that the NIH's broader mandate is to clarify the *NIH Guidelines* as science evolves. Third, absent any mechanism and faced with urgent requests for the use of gene therapy in imminently dying patients, an NIH interim policy must be in place while this issue is thoroughly reviewed and long-term options are developed. Proposed policy regarding this issue should be developed based on input from the members of the RAC, the scientific research community, in coordination with FDA procedures and statutory authorities, and full public dialogue.

Dr. Healy stated that this meeting serves two purposes: (1) to inform the RAC of the interim approach that has been put into place to handle Dr. Royston's request expeditiously; and (2) to develop formal procedures for addressing future compassionate plea requests.

Dr. Healy outlined the interim approach that will be taken by the NIH absent a formal procedure: (1) If an experimental recombinant DNA product proposed for compassionate therapeutic use is derived from research that is subject to the *NIH Guidelines*, NIH has a responsibility to respond to that request. (2) This response must be made in a timely manner consistent with existing practices for compassionate use exemptions for other drugs and biologics. To the extent consistent with the need for rapid action, public notification will occur. In any case, the decision and the basis for the decision will be made public. (3) NIH will gather appropriate information on patient and public safety, including all documents submitted to other review bodies. NIH will seek advice of the appropriate Institute, Center, and Division representatives; other experts; the RAC Chair; and other individuals deemed necessary by the Chair. (4)NIH approval of a compassionate plea request will be contingent on FDA, IRB, and Institutional Biosafety Committee (IBC) approvals.

Historically, the strength of the RAC is that it has always been responsible to the changing nature of science and public concerns. The submission of a compassionate plea request was inevitable. The promise of gene therapy is too great; the needs of the patient community are too desperate.

Dr. Healy stated that in the context of this pressing matter, the RAC is charged with developing recommendations that will provide a long-term procedure for handling compassionate plea requests for gene therapy. In executing this charge, the RAC needs to consider the following questions: (1) What should the scope of the RAC's role be in reviewing non-research compassionate plea requests for gene therapy? (2) How will the circumstances under which a non-research compassionate plea request for NIH approval be defined? (3) Does the RAC, as currently constituted, have adequate expertise to review individual patient requests? (4) How can a time-sensitive mechanism be developed for handling these requests that involves the public? This response must balance the need for public information with the needs of the patient for privacy and timely review. (5) How should the RAC mandate be expanded or enhanced to accommodate this new responsibility?

Dr. Healy concluded her remarks noting that the evolution of the *NIH Guidelines* must reflect the NIH's mission to apply scientific knowledge in order to extend the health of human lives and to reduce the burden resulting from their disease and disability. It is in this spirit that the RAC is asked to undertake this task.

Committee Discussion

Dr. Walters asked if the RAC members' had any questions and comments for Dr. Healy. The committee should focus their discussion on the five questions outlined by Dr. Healy. Dr. Walters recognized the RAC members who were joining the discussion via conference call, namely, Mr. Capron, Dr. Geiduschek, and Dr. Schaechter. Dr. Walters noted the order in which speakers would be recognized. The RAC members will have the first opportunity to respond, followed by liaison representatives, other NIH employees, members of the public who have submitted a formal request to address the committee, followed by the public at large.

Dr. Parkman said that many of the RAC members have had extensive experience with the expedited approval or compassionate use process. He inquired whether compassionate use implies the probability of efficacy. Specifically, is a Phase I study a potential topic for compassionate use? There is a potential ethical and societal difference between therapy that has the probability of efficacy and the rights of all people to have access to that therapy, regardless if the intent is purely experimental.

Dr. Parkman explained that the process for determining the answers to these Phase I compassionate use questions is already in place at the level of the IRB. Many IRBs have a ruling that a compassionate use protocol that presents significant risk has to be reviewed by the full body, whereas a protocol that provides minimal risk can be administratively approved by the IRB Chair using any assistance necessary. It is important that the RAC adopt the same criteria for the assessment of compassionate use protocols for human gene therapy. In addition, the use of the compassionate use mechanism should be granted solely on a one-time basis.

Dr. Krogstad stated that in terms of public perception, the words compassionate use suggests a reasonable expectation of efficacy. During the course of this discussion, the RAC should consider the public's perception. It is unfortunate that Dr. Royston's protocol has brought the issue of compassionate use of gene therapy to the RAC, because this protocol has serious scientific and medical shortcomings. However, Dr. Krogstad supported Dr. Healy's effort to develop a mechanism for the approval of compassionate plea requests.

Dr. Leventhal said that the RAC should discuss whether any patient who is treated under a compassionate use exemption should be considered a research subject. The Office for Protection from Research Risk maintains that such patients cannot be considered research subjects. An investigator who receives a single patient compassionate use exemption cannot include the results of that patient data in any further reports of their research. Considering the public nature of this committee and the great interest in gene therapy, it is going to be extremely difficult not to interpret results.

Dr. Zallen noted the NIH has been particularly concerned about the accessibility of women and minorities to research protocols. She asked Dr. Healy if these same concerns will be applied to compassionate use policies. Dr. Healy stated that compassionate use exemptions are granted on a case-by-case basis. These exemptions are non-research. Although all U.S. citizens should have equal and fair access to research protocols, compassionate use cannot be considered research. Data regarding compassionate use patients may not be part of data that is presented as a generalizable body of knowledge, which is explicitly stated in existing NIH regulations.

Dr. Walters recognized the NIH staff who were present at the table: Mr. Robert Lanman, NIH Legal Counsel; Ms. Sandy Chamblee, Senior Policy Advisor and Counselor to the Director; Dr. John Diggs, Deputy Director for Extramural Research; Dr. John Mahoney, Associate Director for Administration; Dr. Lance Liotta, Deputy Director for Intramural Research; and Dr. Bruce Chabner, Director of the Division of Cancer Treatment, NCI.

Dr. Chabner responded to the issue of efficacy of compassionate use therapy. Safety should be the important consideration, not efficacy. NCI's Division of Cancer Treatment handles numerous compassionate use requests; in many instances, there is very little, if any, information to suggest that the therapy will be effective.

Ms. Buc said that she had several suggestions for separating the RAC's role from NIH's role on this issue. During the course of this discussion, the RAC must consider the role of an advisory committee versus the government. Advisory committees advise and governments govern. The RAC serves an enormously important purpose of exploring, discussing, and providing a wide variety of expertise. But as its name states, the RAC is simply an advisory committee to the NIH Director. The NIH Director has the authority and responsibility to decide on each protocol that is presented to the RAC.

Ms. Buc stated that Dr. Healy had ample legal authority to make this decision. Perhaps more important, she attempted to include the RAC and other individuals in the process. Dr. Healy should exercise her authority to grant compassionate use exemptions for gene therapy, consult the RAC if possible, and notify the public by an appropriate mechanism. Ms. Buc suggested that discussion should focus towards reducing the RAC's formal exposure to compassionate use requests; however, the committee should assist NIH in establishing guidelines for the consideration of such requests.

Dr. Chase stated that he respected the process by which Dr. Healy made her decision regarding Dr. Royston's compassionate plea request. Dr. Chase said that in his opinion, the December 1992 RAC meeting would have been more productive if Dr. Healy had been present. The RAC would have attempted to support Dr. Healy's original position that Dr. Royston's request should not be granted because of both inadequate safety review and the lack of demonstrable evidence that the treatment would be efficacious.

Dr. Healy said that when Dr. Royston's patient was originally brought to NIH's attention in October 1992, no safety data had been obtained. This safety documentation was submitted in December 1992, around the time of the RAC meeting. Dr. Healy stated that her decision to grant this request was based on recent safety data and the advice of NIH staff. Safety was the overriding issue that governed the FDA's deliberations. This informed judgement was based on new information submitted to the NIH and the FDA.

Dr. Walters instructed the RAC members and other NIH officials to examine the 3-page proposal that was developed by the working group on compassionate plea exemptions. Dr. Walters outlined the working group's proposal. The introductory statement of this document explains that the ideal submission and review for compassionate use requests, including single patient protocols, is eight weeks in advance of a scheduled RAC meeting. However, in the event that this time-frame cannot be maintained, the working group proposed the following options: (1) Expedited RAC review, either special meetings between regularly scheduled RAC meetings, or some similar mechanism for reviewing compassionate plea requests that arise between meetings where emergency action is needed. (2) Referral to previously approved protocols; however, the RAC must consider the situation where a protocol already has a long waiting list of patients who meet the appropriate inclusion/exclusion criteria. (3) Allow new investigators to use vectors that have already been reviewed and approved by the RAC for human gene therapy. (4) Consider compassionate use requests outside of the research system and require that data from such treatments cannot be used in research publications. In conclusion, the proposal states that the working group does not recommend any of these alternative mechanisms; because there are serious reservations about each point. The working group has outlined these items so that the entire RAC and Dr. Healy could refine a particular option or propose an entirely new alternative.

Dr. Post said that he agreed with the statement made by Ms. Buc regarding the authority of the NIH

Director to make these decisions. Since the RAC does not readily fit into the compassionate plea request process, perhaps a final alternative should be that the RAC should not entertain these requests.

Ms. Buc stated that she was puzzled by point number 4. There seems to be some kind of punishment intended for investigators using compassionate plea requests; namely, they do not have the opportunity to cite their results. Denying publication to these investigators undercuts an important aspect of our effort; namely, deriving important information from these early experiments. The FDA recognizes that compassionate use requests are not full-blown research; however, their regulations require that investigators must report any information obtained as a result of the procedure. Therefore, the NIH and the RAC should not allow investigators to relinquish their obligation to file a report.

Dr. Healy reminded Ms. Buc that investigators always have the option of publishing a case report. This mechanism allows the investigator to relay new information, but it does not require the statistical validity of a research publication. Dr. Healy stated that compassionate use treatments can be certainly considered valid as case reports.

Dr. Healy reminded the RAC that her comments regarding the non-research component of compassionate use requests were not intended to get the RAC off-the-hook. The RAC should have a role if an experimental therapy is a direct derivative of research conducted and supported by the NIH. The NIH needs the advice of the RAC. How can a system be created in which the RAC can provide advice and balance the needs of a patient that is in imminent danger? In turn, if a patient is not in imminent danger, then the proposal can wait until the next scheduled RAC meeting. Dr. Healy said she has learned during this process that the RAC cannot convene without the appropriate public notice. These are uncharted waters. The flexibility of the RAC is important. If NIH cannot depend on the advice of the RAC then it will have to seek the advice of some other similar body. Dr. Healy stated that advice regarding gene therapy should come from the RAC.

Mr. Capron inquired how the NIH understands the basis for compassionate use exemptions granted by the FDA. Is there any expectation that other review processes would be required, i.e., IRB and IBC review? Dr. Healy responded that the FDA includes the standard review procedures as part of their compassionate use IND process. Dr. Healy reminded Mr. Capron that the NIH did not deliberate with the FDA. The FDA conducted an independent review using the standard procedures for compassionate use single patient INDs. NIH did not make a decision regarding this issue until the FDA had granted approval, because the FDA has regulatory authority and statutory authority. The NIH used the FDA's approval to help guide its decision.

Mr. Capron said that he understands FDA has a process, the question is what is the basis for this process? If the RAC develops a compassionate use process as has been suggested, would the FDA become the only real review mechanism? If an investigator is faced with a lengthy 8-week review mechanism with public scrutiny or the closed-session quick review provided by the FDA, what course would investigator's choose? Mr. Capron stated that he could not imagine that there would be many investigators that would choose the long review process. Maybe the committee should face the judgement that the RAC approval process is in the evolution of the field, as Dr. Healy has stated; and it is no longer necessary. The RAC will no longer be relied upon. At the very least, it would be relied upon in those cases where the research is most justified; where the design of the research and the preclinical work has been fully carried out and is most defensible. In the least defensible cases where those protocols could not pass the RAC's scrutiny, the alternative approach with less public process will be chosen. Mr. Capron said that it is his understanding that Dr. Royston's IBC never granted approval for this compassionate plea protocol. The RAC has not seen the data that was presented to the FDA.

Dr. Healy reminded Mr. Capron that Dr. Royston's request was not viewed as a research proposal.NIH did not grant approval for research to be performed that was not believed to have been adequately reviewed as a research protocol by the RAC. Dr. Healy explained that the phrase, evolution of the field, does not imply that the field has become so advanced that the RAC is no longer needed. This phrase refers to the evolution of human gene therapy, expectations about therapies, and evolution to the patient. Dr. Healy said that she is deeply concerned about the notion that the FDA should be the sole decider of compassionate use exemptions that are derived from research that would otherwise come under the purview of the RAC. There might be circumstances in which the FDA would approve a compassionate use IND, and NIH would deny approval because of concerns about the vector or other safety aspect of the procedure.

Dr. Healy explained that the NIH spent a great deal of time reviewing the safety issues surrounding this particular vector. Drs. Liotta, Chabner, Broder, and others, reviewed Dr. Royston's request repeatedly and the questions were: Are there safety issues? Is there something unique? Is this protocol similar to Dr. Gansbacher's protocol? Doesthe NIH have a basis upon which we would disagree with FDA's conclusion? Upon consideration of these questions, NIH could find no basis for determining that the FDA had made a mistake in granting this approval. However, it would be a mistake for theNIH to state that it would defer all compassionate use requests for gene therapy to the FDA just becauseNIH agreed with the FDA's decision in this case. It would be tragic for the RAC to state that because of one exemption, the committee is no longer needed. The RAC is needed now more than ever as expanded human therapies are being explored.

Dr. Leventhal said that she would like to discuss the use of the word compassionate as it implies to the patient's need for this treatment. The FDA term single patient use is a more preferable description of this procedure. The RAC should protect patients from feeling that they need a particular therapy that has never been proven to provide clinical benefit.

Dr. Krogstad said that he has trouble separating the development of compassionate use procedures from the specific case at hand. It is important to clarify that the circumstances surrounding Dr. Royston's request were created when the original protocol was rejected by the RAC as being inadequate on both scientific and medical grounds. This situation should not erupt again.

Dr. Parkman asked Dr. Chabner if it is appropriate for the first person to receive a novel therapy to be on a compassionate use basis, i.e., there is no supporting data regarding the safety of that therapy in human?

Dr. Parkman reiterated his view that there is no mechanism outside of the current 3 month meeting cycle that allows the RAC to have a formal advisory role. The rules can be changed to allow for expedited review, but that would make the review process private instead of public. The RAC must balance the right of the individual to receive expedited review with the right of the public to be informed about these proposals. Dr. Wivel stated that Dr. Parkman has addressed the essential point; specifically, the*NIH Guidelines* require that the RAC is under obligation to conduct its discussions in public. Notice of meeting has to be given in consideration of the Federal Advisory Committee Act. The public must be allowed to comment on the agenda, and the meeting materials are made public. In the event that the RAC chooses to modify the procedures as they currently exist, they would have to decide if the public should be notified in precisely the same manner as in the past or decide whether gene therapy has reached the level of acceptance that it is no longer viewed as a threat to the safety of the public.

Dr. Chabner responded to Dr. Parkman's question. Dr.Chabner explained that there is always a first patient to receive every therapy, and this usually occurs within the context of an experimental protocol. However, there are thousands of patients who receiveapproval for the compassionate use of drugs under

much different circumstances. Drug use in this country is not necessarily regulated on the basis of efficacy in experimental situations or in compassionate use situations. For example, there is widespread use of a variety of drugs for the treatment of acquired immunodeficiency syndrome (AIDS) that have not been proven to be efficacious in the treatment of this disease. A balance has been struck between the right of an individual patient to have access to an experimental drug or therapy and the concerns of the community about safety. Dr. Healy's decision is consistent with the way that compassionate drug use is being used for diseases such as AIDS.

FDA Statement--Dr. Woodcock

Dr. Janet Woodcock, Director of the Office of Therapeutics of the Center for Biologics Evaluation and Research, stated her intention to clarify some of the questions that have arisen during the course of this discussion regarding the FDA's review of gene therapy. The vectors that are used for gene therapy are classified as investigational biological products. Therefore, vectors used for human gene therapy come under statutory authority for regulating investigational products, investigational drugs, and biologics. The FDA has a defined set of regulations that are followed for the approval of human protocols. A 2-page FDA document was distributed summarizing single patient use and emergency use situations.

Dr. Woodcock stated that the RAC plays an important complementary role to the FDA. The FDA focuses on manufacturing, i.e., the production of these experimentalbiologicals. The FDA does not always provide the opportunity for open public discussion that the RAC permits.

The FDA's review of any investigation protocol in humans includes an assurance by the investigator and an understanding that any applicable regulations, policies, or approvals, have been obtained and followed including IRB, IBC, and RAC approval, if appropriate.

There has been increasing pressure from patients, patient advocacy groups, and the general public, to increase access to experimental therapies earlier in the investigational stages. Traditionally, this access has been limited to drugs that were late in the development cycle. However, over the last 5 years, especially in human immunodeficiency virus related illnesses and cancer, there has been increasing pressure and response by the FDA to provide access to patients earlier in drug development. The FDA provides these therapies with the understanding that patients may be exposing themselves to the increased risk of toxicity. In addition, these patients may be deferring themselves from another more effective therapy that might be available.

Dr. Woodcock stated that the FDA encourages access to these drugs; however, the FDA discourages access before the agent has been tested in a Phase I trial because of uncertainties about the dose/toxicity profile of the drug. Many drugs that seem promising in the preclinical development phase are abandoned following a Phase I trial due to toxicity. However, the FDA still receives occasional requests for exceptions from patients who have exhausted all other therapies, do not fit the inclusion/exclusion criteria of the protocol, do not have geographic access to the protocol, or for other various reasons. In these rare cases, the FDA tries to work with the patient's physician and the investigator to provide some exception. Most of these cases are time-limited situations due to the life-threatening status of the patient.

Dr. Woodcock explained that the emergency use situation is more of a medical emergency in which there is insufficient time to perform the required paperwork. Physicians can call the FDA and request clearance for emergency use. Emergency use would ordinarily occur when there is some known effectiveness information about the agent, and there is a clear indication why the physician made the determination that the particular agent was needed.

Committee Discussion

Dr. Walters inquired as to the particular section of the FDA regulations that encompasses the single patient use category. Dr. Woodcock responded that the correct terminology is single patient IND which is found in section 312 of the 21 Code of Federal Regulations. An IND application exempts the sponsor from the general requirement to use an approved drug.

Dr. Parkman asked if the requirement for the submission of preclinical data is different for single patient protocols than for multiple patient protocols. Dr. Woodcock explained that virtually the same standards for submission data are required for both types of requests. However, the FDA statutory and regulatory regulations do not apply the same standards of preclinical rationale that the RAC requires.

As a point of clarification, Dr. Post inquired whether the FDA has granted first time use of investigational protocols on a single patient basis. Dr. Woodcock answered that the FDA has granted first time single patient use; however, these instances have been extremely rare.

Dr. Post explained that many of the RAC members are concerned that Dr. Royston's protocol was approved based on the documentation that was submitted to NIH. He asked Dr. Woodcock to provide the committee with qualitative information about the kinds of data that the FDA considered before granting approval of this request. Dr. Post stated that the members of the RAC would have more confidence in this decision if they could be assured that Dr. Royston submitted significant documentation, other than the information sent to the NIH. Dr. Woodcock said that she could define the FDA's criteria for approving a gene therapy biologic for a Phase I trial. Dr. Post asked Dr. Woodcock to be as specific as possible about this particular approval. Dr. Woodcock said that she could not provide that information. Dr. Post asked Dr. Royston to respond to this question during his statement.

Dr. Woodcock stated that the vector proposed by Dr. Royston was already approved by the NIH and the FDA. Dr. Post said that the vector had been approved for use in Dr. Gansbacher's protocol. However, the cells have not been approved, which is an important distinction. Dr. Woodcock stated that any concerns the RAC would have about the cells probably focus on the activity and effectiveness of the cells rather than biosafety considerations. Dr. Post said that the safety of these cells is a primary consideration.

Dr. Woodcock stated that it is plausible that the RAC and the FDA would come to different conclusions. In fact, on every single gene therapy protocol the FDA has reviewed, there has been internal scientific disagreement. Dr. Royston's request is a sort of hybrid request because of the element of the cells. The investigational vector has been approved for a Phase I trial. However, the use of this vector was not simply an extension at a different geographic site. Obviously, Dr. Royston proposed to use the vector in a different manner than Dr. Gansbacher.

Dr. Geiduschek asked Dr. Woodcock if the FDA's approval of drugs that have never been approved for investigational use refers to the U.S. or anywhere in the world. Dr. Woodcock responded that these rare exemptions have been granted for drugs that have never been used in any Phase I trial in the world. However, the FDA is very discouraging about such uses, because there is no evidence of efficacy and no toxicity data is available on these agents.

Dr. Geiduschek asked for clarification regarding the criteria that the FDA uses to grant such approvals. Does the FDA grant compassionate plea exemptions for materials whose properties in humans are unknown? Dr. Woodcock responded that the FDA requires the same safety information whether the protocol is directed toward a specific patient or a total Phase I trial.

Dr. Haselkorn asked Dr. Woodcock if the FDA was provided any information on the safety of the transduced cells to be used in Dr. Royston's protocol. Dr. Woodcock said that the FDA outlined their requirements for safety testing previously, both for adventitious agent testing and for expression of the desired gene. Every lot of investigational biological agents administered to humans must meet a set of lot release criteria. These criteria are primarily safety and potency testing. Dr. Woodcock saidthatshe is not authorized to discuss this specific case in detail.

Dr. Leventhal inquired whether each autologous tumor cell preparation constitutes a lot. Dr. Woodcock said that the requirements for testingautologous cells are less stringent than for other biologics because of technical limitations.

Ms. Meyers stated that she is a public member on this committee who represents individuals with rare diseases, the majority of whom are as desperate as Dr. Royston's patient. She expressed concern about the criteria that the FDA uses to grant single patientINDs. Patients with AIDS and cancer are granted permission routinely to take drugs that are not approved and that are in the early stages of testing. However, the FDA stopped the production of a drug that was being produced by an investigator at Johns Hopkins University because of failure to pass good manufacturing practices. This drug, which was routinely manufactured for years, has kept hundreds of children alive who were diagnosed with a rare disease. Apparently, what is true for certain politically important groups is not true of the politically unimportant groups.

Ms. Meyers stated that her recommendation is that the RAC should send a letter, which includes recommendations on policy, to the incoming administration. There is no reason that the RAC should be forced into taking any action on this issue prior to January 20.

Ms. Meyers explained that there is an enormous difference between drugs and gene therapy. If a patient is adversely affected by a drug, only that patient is usually affected. With gene therapy, nothing is known about the long-term affects to the patient, health care workers, the patient's spouse, or the next generation

Ms. Meyers explained that the Foundation for Economic Trends has gone to court in order to ensure that gene therapy deliberations are held in public, because society has a great stake in the outcome. However, the RAC is being urged to turn away from the public and allow these decisions to occur in private.

Ms. Meyers said that Dr. Royston's patient is not an inpatient. Therefore, she is allowed to go out into the public following treatment. The FDA approval of this protocol is analogous to approving an envelope without knowing the message of the letter. The members of the RAC are the experts that know what that message should be and the potential danger that can occur if that message is incorrect. The RAC was completely cut out of this approval process.

Ms. Meyers explained that Dr. Royston's protocol was deferred in 1991 because he was not prepared. The RAC told Dr. Royston to perform additional experiments. In 1991, Dr. Royston did not even have a patient in mind; he wanted to rush at that point. Dr. Royston said in November 1991 that he would resubmit his protocol in 3 months; henever resubmitted the protocol. The RAC never heard from Dr. Royston until he returned to NIH with a request for a compassionate plea exemption. The RAC has still never received a complete submission. The information submitted to theNIH is completely unsatisfactory.

Ms. Meyers stated that the informed consent document that Dr. Royston's patient signed was untruthful. Dr. Royston has continually stated that, this is the patient's last chance, even though every piece of information submitted to the RAC indicates that this protocol will provide no therapeutic benefit. Dr.

Royston's patient will not benefit from this treatment. The approval of this one compassionate plea reques will open the door to thousands of similar requests, all asking to receive gene therapy that has not shown any effectiveness at all.

Dr. Chase said that there are aspects of this particular case that make consideration of the general problem difficult. These aspects are as follows: (1) there is the issue of equity of access; (2) there is a lack of public scrutiny regarding the ultimate decision process; (3) public involvement has been eliminated, which is an important principle underlying the function of the RAC; (3) there is a lack of scientific evidence supporting efficacy of the treatment; (4) there is the possibility that these extraordinary steps were taken in order to evade a more stringent review; and (5) there has been a derangement of normal Federal government processes.

Statement--Dr. Royston

Dr. Walters called on Dr. Royston to respond to the RAC members' questions and comments. Dr. Walters encouraged Dr. Royston to provide a productive and constructive interchange. Specifically, was there any information that was submitted to theNIH, the FDA, or both agencies, after the December 1992 RAC meeting that contributed to the decision-making process?

Dr. Royston stated that he was appalled by the comments that have been made by the members of the RAC. He said that he is trying to comply with every Federal regulation and the*NIH Guidelines*; there are no base motives. He said that he worked an entire weekend on the*Points to Consider*, only to be informed that approval had been granted by theNIH Director.

As a point of clarification, Dr. Royston said that the protocol submitted in November 1991 is different from this protocol. He stated that it is his intention to submit the revised gene therapy protocol to the RAC in 1993, as soon as the vectors are certified by the FDA. Dr. Royston stated that he does not want to rush to bring in a protocol, he wants to be methodical and careful.

In the interim, Dr. Royston said that he was able totransduce and grow this particular patient's glioblastoma tumor cells in culture. This procedure is no mean feat. The question was, can we help this patient? This patient is an individual with a Stage IV glioblastoma who has failed all conventional therapies. Therefore, the only therapy available to this patient is experimental therapy. It is right that she receive this treatment. This individual is a thriving woman who has a life expectancy of 1 to 2 months, who otherwise functions normally.

Dr. Royston stated that he is a physician and a medical researcher. He receivesNIH grants; therefore, he does not intend on evading the RAC. However, if it comes to choosing between a physician and a researcher, he is a physician first. He wants to give his patient the best available therapy.

Dr. Royston explained that based on the scientific literature, there is a strong rationale for providing this patient with genetically modified, transduced glioblastoma cells. All of the additional data that the FDA requested was submitted. However, he is not prepared to present this additional data today. Dr. Royston said that he would present the scientific rationale for this study and all of the data submitted to the FDA at the March 1-2, 1993, RAC meeting. Dr. Royston commended Dr. Healy for granting approval of this compassionate use request.

Dr. Krogstad asked for clarification regarding the submission of additional material. Was additional material submitted to the FDA that was not submitted to the RAC? Dr. Royston acknowledged that this

statement is correct. The following additional safety data was submitted to the FDA: (1) replication competent retrovirus data, (2) sterility data, (3) data on the transduced cell line, (4) data demonstrating the lack of contaminating helper virus, and (5) vector identity data.

Dr. Krogstad inquired how interleukin-2 (IL-2) production in transduced cells compared with the experimental data that the RAC reviewed. Dr. Royston stated that the RAC did not have access to the experimental data. Dr. Royston said that the transduced glioblastoma cells secrete 30 units of IL-2 per 2 x 106 cells per 24 hours.

Dr. Krogstad said that there is merit to having the RAC review the data on which this single case exemption was granted, even retrospectively, to satisfy the concerns that have arisen among the committee members. Dr. Royston explained that the RAC's concerns have to be weighed against the needs of individuals. Dr. Krogstad said that he understands these considerations, because he has been a physician for over 20 years. Dr. Krogstad said that the patient's interests must be paramount; however, there is no excuse for overlooking the need to review these other issues.

Dr. Royston said that he would provide the RAC with any data that it believes is important to review. He does not want the RAC to accuse him of being evasive. Dr. Post said that he would like to take Dr. Royston up on his offer to provide the material that was submitted to the FDA which was never submitted to the RAC. Dr. Royston agreed to provide the FDA material for the March 1-2, 1993, RAC meeting.

Dr. Post stated that the RAC will make an exception to the January 4 submission deadline because the protocol is not under formal review. Submission of this additional information will suggest the mechanism that was used to approve this protocol. The record can be set straight, rather than continue the guesswork about what information was submitted to the FDA. Perhaps review of this additional information at the March 1993 meeting will evolve into a constructive process.

Dr. Geiduschek asked about the specific protocol that was reviewed by the San Diego Regional Cancer Center's IRB on December 18, 1992. Was it the transduced fibroblast protocol or the transduced glioblastoma tumor cell protocol? Dr. Royston responded that the IRB primarily reviewed the transduced glioblastoma protocol; however, it was requested that if the number of glioblastoma cells was insufficient, then fibroblasts could be used instead. Dr. Geiduschek asked if the material that was provided as part of the RAC mailing was the same material that was supplied to the IRB. Dr. Royston said that he could not recall if the same material was presented to the IRB. The protocol underwent several modifications.

Dr. Royston explained that the final protocol was never sent to the NIH. Dr. Geiduschek asked if the final protocol was substantially different from the original protocol. Dr. Royston said that it depends on whom you ask. The only significant difference is that the dose of radiation was lowered from 20,000 rads to 7,000 rads.

Dr. Royston said that the protocol that was submitted to NIH was written after returning from the December 1992 RAC meeting. At that meeting, the RAC said that they would entertain a single patient protocol. He stated that Dr. Wivel had requested that additional data should be submitted, including the Points to Consider, but was informed that the application could be withdrawn following Dr. Healy's approval. Dr. Royston said that he would supply this information for the March 1-2, 1993, RAC meeting.

Ms. Buc suggested that Dr. Royston should present the material that was submitted to the FDA at the March 1993 RAC meeting, not for formal review, but as a special presentation. Ms. Buc stated that she is extending a formal invitation to Dr. Royston to present this information at the March 1993 meeting. Ms. Buc stated that since Dr. Royston has accepted the invitation to return in March 1993, the RAC should

turn to the question to how these compassionate plea requests will be handled in the future. Should these requests come to the RAC or a subset of the RAC? Should the NIH Guidelines be amended? These questions must be answered within the context of the Federal Advisory Committee Act; however, Ms. Buc stated that this act may include provisions for emergency exceptions.

Ms. Buc said that the RAC must consider a number of questions. What constitutes an emergency exception or a single use exception? What are the criteria for these exceptions? What are the criteria that NIH should use in acting on these situations? What will the RAC's role be in this process? Should the number of RAC meetings increased? How should the NIH respond to a patient that does not fit into the criteria that will be established?

Ms. Buc stated that she was concerned about some of the statements that were made regarding the qualifications of the FDA and the RAC. The RAC is comprised of members who possess significant expertise. However, she stated that she has considerable confidence that the FDA can handle these compassionate requests on a single patient basis. It is unfair to say that only the RAC has the scientific competence to review a vector or a protocol.

Dr. Leventhal urged the RAC to defer any further discussion of the individual protocol; the remainder of the meeting should be dedicated to developing general policies on the issue of compassionate requests.

Dr. Carmen asked Dr. Royston how he would respond to the multitude of patients suffering from glioblastoma if they requested the same therapy that this woman received. Dr. Royston responded that he has already received approximately 100 requests, and that he referred these patients to Dr. Oldfield's protocol. Dr. Royston said that the NIH will now have to deal with compassionate requests for Dr. Oldfield's protocol.

Dr. Zallen noted that this compassionate request resulted from the rapid progression of this patient's disease. The RAC was informed that the 3 month period between meetings was too long for the patient to wait for treatment. However, the informed consent document is dated August 10, 1992. If Dr. Royston had requested RAC review of the protocol on this date, there would have been enough time to proceed through the standard RAC review process, i.e., at the December 1992 RAC meeting. Dr. Royston said that the reason for the delay was because of his misunderstanding regarding the availability of single patient protocol review by the RAC. Dr. Royston stated that a lot of things are easier in hindsight. In retrospect, the proposal probably should have been submitted as a single patient protocol before the deadline. Dr. Zallen explained that it is useful for the RAC to consider that had Dr. Royston been aware that there was a mechanism for the review of a single patient protocol, he could have met the submission criteria without the need for an alternative mechanism. Dr. Royston responded that if the committee had rejected the protocol on the basis of insufficient data and FDA approval had been obtained, he would have urged the NIH Director to approve the request in any case.

Committee Discussion

Dr. Krogstad stated that it is impossible to remove cells from a patient, grow them up, transduce them, and demonstrate their safety within 24 hours. Therefore, there should never be a need for the RAC to turn such a request around in 24 hours. If the investigator initiates the RAC review process at the time the cells are removed with the intent of transducing them, there always will be sufficient time to provide thorough review.

Dr. Parkman explained that RAC review of human gene therapy protocols generally evolves around three areas: the vector(s), the cells that will be transduced, and the laboratory in which the transduction will

occur. To say that the same vector and the same cell type can be used in another investigator's laboratory is unacceptable. The RAC has never defined a protocol solely in terms of the subject(s). Although the RAC may choose to entertain single patient versus multiple patient protocols differently, the criteria should remain the same. If the RAC chooses to provide expedited review, then speed becomes synonymous with non-public review. The *NIH Guidelines* can be amended to accommodate non-public review; however, the RAC will become vulnerable to criticism from those individuals that believe strongly in public review of gene therapy. He stated that he is uncertain how the RAC should balance speed and efficiency against the public's rights to access.

Dr. Post commented that if the public component becomes non-existent, then should the RAC exist? Dr. Parkman stated that even if the RAC chooses to review single patient protocols differently from multiple patient protocols, the criteria for such review should remain constant even though the process for reviewing these proposals may differ.

Mr. Capron agreed with Dr. Parkman's description of the objectives; namely, to maintain competent standards. The RAC is a deliberative body which incorporates external review. This type of review is not easily adapted to the kind of process that Dr. Royston has suggested is necessary. Mr. Capron responded to the questions that were posed by Dr. Healy during her statement to the RAC: (1) What is the scope of the RAC's role in reviewing non-research compassionate pleas for gene therapy? Mr. Capron said that the expedited review process will have to rely on a different form of advice, which does not ensure public scrutiny. The design of the research that the RAC has traditionally been concerned about is irrelevant in a non-research situation. (2) What are the circumstances under which non-research compassionate pleas ought to require NIH approval? The NIH will have to determine the criteria for answering this question, not the RAC. (3) Does the RAC, as currently constituted, have adequate expertise to review requests for individual patients involved in recombinant DNA intervention? The implication is that the RAC does not know how to review protocols that involve patients. There is an appropriate combination of expertise on the RAC. Individual patient requests differ from multiple patient requests only in that the design of the research and its potential to contribute to general knowledge is absent. (4) How can a time-sensitive mechanism be developed for handling such requests? Mr. Capron said that expedited review will probably have to come from the FDA and the NIH Director. (5) How can the RAC mandate be expanded or enhanced? Mr. Capron said that the results of these single patient protocols should be reported to the RAC. The RAC should have access to any data relating to safety or problems associated with the procedure.

Dr. Leventhal said that she was uncomfortable with the terminology single patient protocol because some of these protocols might be considered research. There may be genetic diseases so rare that there is only one person available in whom an important experiment can be performed. Therefore, single patient research protocols must be distinguishable from single patient non-research protocols. The RAC members have indicated that safety needs to be assured in either setting. However, in a non-research setting, a single patient may be given material without the strict review and the possibility of efficacy required for a research protocol. She stated that she would not accept the approval of any experiment in which the results were not reported to the RAC.

Dr. Geiduschek continued, stating that the RAC as a national public committee on human gene therapy, has a natural time limit. There will come a point in which the kind of review currently undertaken by the RAC will be deemed no longer necessary, and the committee will be abandoned. Until that time, the dual system of approval, namely, research versus non-research compassionate use, is not appropriate or in the public interest. Compassionate use should only be approved in the context of the working group's recommendations, i.e., expansion of the inclusion/exclusion criteria of a previously approved protocol. If the RAC chooses to grant compassionate use exemptions within the context of approved protocols, clear

eligibility requirements, including the patient and the physician, would have to be established.

Dr. Geiduschek recommended that the retrospective examination of Dr. Royston's protocol will be helpful in bringing the RAC to an agreement on future policy. He agreed with the statement made by Mr. Capron; namely, that the qualifications of the RAC members are appropriate for the review of both single patient and multiple patient protocols.

Dr. Geiduschek asked for the opportunity to state his views before having to leave the telephone conference. He referred the RAC to his written statements and emphasized that these statements represented his best judgement at that moment, as they had in advance of the meeting.

Dr. Parkman said that he disagrees with Dr. Healy's concept of a non-research protocol. Any patient that receives gene therapy will be treated at an institution that has an ongoing gene therapy research program. The issue is that there is a patient who intersects with those research interests and the time frame for instituting therapy does not fit within the time constraints of the RAC. Therefore, the term single patient protocol is appropriate to describe these situations. Although statistical evaluations will not be possible, statements can certainly be made regarding efficacy.

Statement--Ms. Katherine Matthews

Dr. Walters called on Ms. Katherine Matthews, staff attorney for biotechnology, of the Foundation on Economic Trends, to present her statement to the RAC. Ms. Matthews distributed a proposed amendment to the *NIH Guidelines* regarding the issue of compassionate plea requests. The Foundation on Economic Trends is concerned that as progress is being made in gene therapy, public review and scrutiny, is decreasing. The Foundation on Economic Trends represents the public interest. The particular case that has brought the issue of compassionate use before the RAC is outrageous; the worst possible case scenario. Undue political influence is very clearly present in this case.

Ms. Matthews stressed the importance for adopting an amendment to the *NIH Guidelines* that will prevent this problem from occurring in the future. The RAC needs to address the question of how the committee is going to deal with the reality that the NIH Director is a political appointee.

The proposed amendment to the *NIH Guidelines* that was distributed by Ms. Matthews could not be voted on at this meeting because it had not been published for public comment in the *Federal Register*. However, Ms. Matthews suggested that the RAC might choose to consider the proposed amendment at the March 1993 RAC meeting. Gene therapy is still in its infancy and does not have public understanding. The need to reassure the public that the process is being scrutinized by all sectors of society is critical.

Ms. Matthews stated that there would be grave concerns on the part of the Foundation on Economic Trends if gene therapy deliberations were to occur in a manner different from what is prescribed in the *NIH Guidelines*, namely, providing the opportunity for public comment.

Ms. Matthews outlined the following proposed amendments to the *NIH Guidelines*: (1) Section I-A reads, ...administration of gene therapy to human subjects... will be amended to read, ...administration of gene therapy either to a group of human subjects or to a single human subject..., (2) A new paragraph will be added to Section I-A to read, ...Any request for compassionate plea exemption to the procedures of these *NIH Guidelines*, see Section III-A, or request for any such emergency use of gene therapy in a human subject or subjects, shall be directed to the NIH RAC in the manner prescribed in these *NIH Guidelines*, see Section III-A, and shall comply with all public notice procedures.

Ms. Matthews stated that if there is any diminution of the public access to RAC deliberations in contravention of the existing law, the Foundation on Economic Trends would file a law suit against the NIH.

Statement--Dr. Henry Miller

Dr. Walters called on Dr. Henry Miller of the FDA to present his statement to the RAC. In the years since Asilomar, recombinant DNA has been defined and circumscribed as an area that requires special attention and regulation. Superimposing this additional regulation has introduced inevitable delays and regulatory disincentives for many activities involving recombinant DNA. There are essentially four layers of regulation for gene therapy: IBC approval, IRB approval, NIH approval, and FDA approval.

In much of the rest of the Federal government, there has been a move to stay away from imposing a separate, discreet, regulatory, paradigm for recombinant DNA. If Dr. Royston's compassionate request had been for a biologic other than gene therapy, the protocol would not have required evaluation by his IBC or the RAC. There may be subsets of gene therapy that may be relegated only to the usual, very comprehensive, very meticulous, methods of evaluation that can be accomplished by the local IRB and the FDA. The RAC should identify some of these rationally circumscribed subsets of gene therapy protocols.

Statement--Husband of Dr. Royston's Patient

The husband of Dr. Royston's patient introduced himself to the members of the RAC. He added that he did not come to this meeting to be critical of the RAC or to try to bury it. As a point of clarification, the patient's husband stated that the informed consent document that was dated August 10, 1992, granted permission to Dr. Royston to grow his wife's tumor cells in culture. The informed consent document did not grant permission for the gene therapy protocol. His wife was granted a compassionate plea exemption, both by the FDA and the NIH. Therefore, he is not trying to obtain anything additional for her. What Dr. Healy did was not only thoughtful and compassionate, but clearly legal.

He stated that he is a lawyer and is quite knowledgeable in the biology of his wife's disease. He became deeply involved in his wife's therapy, i.e., radiation treatments, in January 1992. He was aware of the RAC through the *Federal Register* but was not able to reach anyone at the NIH. He said that he is not suggesting that RAC meetings should not be open to the public. However, the RAC does not have to have the responsibility for compassionate plea exemptions if it does not choose to entertain these requests. Even if the RAC chooses to review compassionate plea requests, that authority can be taken away from the RAC.

Under the Federal Advisory Committee Act (as interpreted by Dabney vs. Reagan in 1992, in the Federal District Court of New York) the head of the agency who appoints an administrator does not have to call meetings. Therefore, the head of an agency that has an advisory committee does not have to call, listen, nor have put before that advisory committee, any matter of any kind whatsoever. He stated that his wife's request has turned into a turf battle.

There is one matter that he found particularly reprehensible; namely, the suggestion that there has been political interference with the RAC and its decision making process. For the record, he explained how Senator Harkin became involved in his wife's compassionate plea for gene therapy. He contacted a former friend and client asking for assistance. This friend said that he knew Senator Harkin from Iowa. The patient's husband informed his friend that his wife is from Iowa and that her family still lives in Iowa. In fact, his wife's sister-in-law worked on several of Senator Harkin's campaigns.

After the appropriate contacts were made, Senator Harkin sent a letter to Dr. Healy on October 8, 1992, requesting that his wife be considered for the compassionate use of gene therapy. This letter had been misconstrued as a threat to Dr. Healy that Senator Harkin would introduce pertinent legislation if the request was not acted upon. The patient's husband assured the RAC that Senator Harkin had not intended this letter as a threat; the Senator had merely offered his assistance. On October 20, 1992, Dr. Healy responded to Senator Harkin's letter stating that the RAC does not have a mechanism by which to consider individual compassionate plea exemption requests. The patient's husband stated that at this point there was insufficient time to submit a protocol within the 8-week time frame. Throughout this entire period, the FDA was extremely cooperative. He will always be grateful to the FDA for their cooperation. These are the facts surrounding any political involvement. He has never talked to Senator Harkin directly and, to the best of his knowledge, no one else with political influence has been involved in his wife's case.

He explained that between himself and his wife's doctors, contacts were made in Canada, England, Germany, France, Italy, and Japan. He has talked to individuals at 31 cancer centers and has spent over $18,000 of his own money seeking treatment for his wife. His wife's tumor was identified on January 10, 1992. Her first resection was on January 14, 1992. She has received 36 radiation treatments, 16 magnetic resonance imagings, 5 computerized tomography scans, etc. On August 10, 1992, she had her entire righttemporal lobe removed. While Dr. Royston was attending the December 4, 1992, RAC meeting, the patient was informed that her tumor had increased in size by 30% in 2 weeks.

The patient's husband explained that he provided this background information regarding the course of his wife's disease to stress the importance of considering the time table involved in these crucial cases.

Statement--Dr. Robert Sobol

Dr. Robert Sobol of the San Diego Regional Cancer Center introduced himself as the co-principal investigator on this single patient gene therapy IND. He stated that he is here to share his perspectives regarding compassionate plea approvals in the hope that his views will be useful in formulating more effective RAC policies for gene therapy in the future.

Dr. Sobol said that he and Dr. Royston had hoped to follow the standard RAC and FDA review process; however, expeditious action was prompted by the deterioration of his patient's clinical condition. This patient has failed all conventional and experimental therapies. Dr. Sobol commended the FDA and Dr. Healy for their rapid responses to the compassionate plea request.

Dr. Sobol explained that the only reason that he did not obtain approval from the RAC is that the committee does not meet often enough. Currently, the portal of entry for Federally supported gene therapy protocols to the RAC is four times per year. These meetings are too infrequent. If the members of the RAC believe it is necessary to review all gene therapy protocols, then they must be prepared to meet more frequently to accommodate these patients. The RAC should also develop guidelines for the review of protocols that reflect modifications of previously approved studies.

Committee Discussion

Dr. D. Miller asked Dr. Sobol why the RAC never received the *Points to Consider* responses or the materials that were submitted to the FDA. Dr.Sobol said that it was the investigators' understanding that this information was not germane to NIH's decision regarding the protocol. However, Dr. Sobol stated that the *Points to Consider* and the FDA submission material will be provided and discussed at the March

1993 RAC meeting.

Dr. Royston reminded Dr. D. Miller that it had never occurred to him that the RAC would entertain a single patient protocol. Dr. Royston explained that the *Points to Consider* responses were prepared in advance of receiving approval from the NIH Director. Dr. Royston said that the *Points to Consider* responses are in his office.

Dr. Zallen noted that Dr. Royston has stated that if he had known it was possible to request RAC review of a single patient protocol, he would have made that request. Dr. Zallen asked Dr. Sobol if he believed that was the case. Dr. Sobol said that he did not feel that Dr. Royston's statement was true, given the time frame involved. Dr. Zallen reminded Dr. Sobol that he had obtained the patient's tissue in August of 1992. Dr. Sobol agreed that the patient's tissue was available, and it was their intention to request RAC review at that time. However, the patient's clinical condition deteriorated, and they were unaware that the RAC would review a single patient protocol. Dr. Sobol said that it is his understanding that the patient's clinical deterioration precluded submission of the protocol in time for consideration.

Dr. Royston stated that a significant amount of time elapsed between the time that the patient's cells were transduced and gene expression was demonstrated. Approval would not have been possible from the RAC in November 1992 because pertinent data was not available. Adequate data was not available until December 1992, at which time the December 4, 1992, meeting had already passed. Dr. Sobol acknowledged that the earlier conclusion, namely, that the investigators could have pulled the relevant information together in time for the December 4, 1992, meeting, was not a correct statement.

Statement--Dr. Williams

Dr. Walters called on Dr. R. Michael Williams to present his statement to the RAC. Dr. R. Michael Williams introduced himself as the Chairman of the Cancer Consulting Group, Professor of Medicine at Northwestern University, and Chief Medical Officer of the Cancer Treatment Centers of America. Dr. Williams explained that he is a practicing oncologist with a Ph.D. in immunology.

Dr. Williams stated that he is in support of Dr. Healy's decision to grant a compassionate permit for the use of gene therapy at the San Diego Regional Cancer Center. Dr. Williams said that he sees the devastation and the hopelessness that cancer brings to families every day. Dr. Williams stated that the RAC needs to be open to new ideas and respond to new therapies quickly. Every avenue and every possibility to offer hope and to save lives should be pursued.

Previous speculations, which raised fears about biological disasters emanating from gene research, have simply not come to pass. Discussions can and should continue, but people die every day from cancers that might be treatable by gene therapy-based techniques. Cancer patients have the right to be empowered as part of the treatment team that decided which therapy is right for them. Compassionate use of a therapy is just that, compassion.

Dr. Williams urged the RAC to exercise compassion in every case they examine. The committee should not adopt guidelines that will slow progress or block options. The RAC should not close any doors.

Committee Discussion

Dr. Walters called on Ms. Buc to propose a motion in an attempt to move the RAC towards the adoption of a policy statement regarding expedited review of time-sensitive gene therapy protocols. Ms. Buc said that many comments have been made throughout the day by RAC members and others that can possibly be

made into a common thread. The RAC is in agreement that it will consider single patient protocols; this issue is undisputed. She said that she would not attempt to make a distinction at this stage of gene therapy between research and therapy. Information can be obtained from these single patient protocols, even if there is no inherent statistical information resulting from these protocols.

Ms. Buc stated that the RAC is in agreement that the criteria are the same for single patient and multiple patient protocols, namely, the concern about safety. These criteria for safety and efficacy are flexible. If the therapy is apparently safe and the plight of the patient is desperate, individuals are more willing to grant approval. However, if safety is a concern and the patient is less desperate, the review may be more stringent.

Ms. Buc suggested that the NIH should publicly state that it has a very strong preference for the submission of protocols to the RAC; however, in emergency situations, NIH will review requests and apply the same criteria as the RAC. Obviously, such a public statement by the NIH will create a multitude of requests. NIH will have to make these determinations independently, applying the aforementioned criteria. The NIH should present a report at the next RAC meeting explaining what decisions have been made and the basis for those decisions. This report will allow for public participation and review. If the NIH's decisions are not a rough proxy of the decisions that would have been made by the RAC, then there will be divergence. If divergence occurs, public opinion will act to reduce that divergence in one way or another. In a sense, the RAC will act as peer review for NIH's decisions. In this way where the situation is critical, there is a safety valve.

Ms. Buc explained that as time passes, the RAC may decide to review fewer of these single patient protocols under some other more specific set of criteria, i.e., derivative of some other protocol. The NIH will handle compassionate plea requests; however, the RAC may choose to examine these decisions. The RAC should request that NIH agree in advance to provide a report following approval of these requests.

Committee Motion

Ms. Buc moved that the aforementioned recommendation is the consensus of the RAC. The motion was seconded by Dr. Parkman.

Ms. Meyers stated that she did not agree that any experiment should go forward without review and recommendation by the RAC. The RAC may recommend that a protocol should not be approved, and Dr. Healy will have the authority not to accept the RAC's advice. However, the protocol should still be reviewed by the RAC for the sake of public discussion. No protocol should be approved without RAC review. She stated that she had also been a member of the HGTS, which voted itself out of responsibility. Ms. Meyers said that everyone hopes that the RAC will eventually be unnecessary; however, the RAC is still needed to assure that the NIH Guidelines are followed. The need for public discussion of every single protocol is still necessary.

Dr. Krogstad addressed the issue of time. He recognized the fact that a patient's status can change radically within a short period of time; however, cells cannot be transduced, cultures defined, and assays performed within a matter of days. One possible approach would be for the investigator to notify the RAC at the time a patient is asked to sign the informed consent document granting permission to transduce their cells. The burden is placed on the investigators at the time they are considering transduction to notify the RAC.

Dr. Schaechter noted that he would not be able to remain on the telephone conference for the remainder

of the meeting; however, he gave the RAC his proxy vote in favor of Ms. Buc's proposal.

Dr. Post said that he is in support of Ms. Buc's motion. It would be a very exceptional that approval of a protocol would happen before a RAC meeting. The proposed mechanism would still allow for public review, at most 2-3 months after the date that approval was granted. There would be a continual calibration of the RAC's standards versus the NIH Director's standards.

Ms. Buc explained that the real constraint on the RAC approval process is that the RAC is subject to a variety of statutes, guidelines, and regulations, that do not allow the committee to function in the same way that a government agency functions, i.e., to take executive action. The RAC has to deal with problems associated with establishing a quorum.

Ms. Meyers stated that the Federal courts have found that gene therapy must involve public disclosure. Ms. Buc said that the Federal courts have stated that advisory boards must function in public; however, there has never been a ruling regarding the necessity to seek the recommendations of an advisory board. The Federal government has the power to govern and to choose when it will seek the advice of an advisory committee. Ms. Buc said that she is confident that the NIH Director will adopt the policy that she has proposed.

Dr. Parkman said that under the proposed policy, the only circumstance in which a protocol would be reviewed outside of the RAC is when there are time constraints that do not permit the normal review process. Therefore, the question is: who will review the protocol? Assuming that these requests are not too numerous, the NIH Director could choose to use RAC members as reviewers of these protocols rather than NIH staff. Using RAC members as reviewers would introduce consistency in the review process.

Ms. Meyers proposed an amendment to the motion. Upon announcement of this policy, the NIH Director will consult (if at all possible, both legally and practically) with current, former, and possible future members of the RAC.

Dr. Parkman said that one of the issues that could arise is the appropriateness of a protocol. There will be some protocols that, by the nature of the subject matter, are really not appropriate for expedited review. These decisions should closely tie to the procedures in effect at the IRB level.

Ms. Buc restated the amendment. The amendment is that the RAC recommends to the NIH Director that when this policy is announced, the Director will announce her intention to consult (to the extent legally and practically feasible) with the members of the RAC and others who can shed scientific, ethical, and legal guidance on the issue in a rapid manner. Dr. Moskowitz noted that this amendment is almost identical to the interim policy created by Dr. Healy and reminded the RAC that an attempt was made to contact Dr. Walters regarding Dr. Royston's approval. Dr. Parkman reminded Dr. Moskowitz that an attempt had been made to notify Dr. Walters that the decision had already been made, not to seek advice.

Dr. Carmen inquired about the legal standing of any vote that is taken by the RAC today. Dr. Walters responded that a quorum vote would be in favor of policy recommendation, which would go forward to the NIH Director.

In response to concerns raised by Dr. Carmen, Ms. Buc amended the policy statement that the NIH Director will take into account, among other factors, the degree of consanguinity to previously approved protocols. The further away the protocol is from a previously approved protocol, the greater the likelihood that it should be brought before the full RAC.

Dr. Carmen stated that the various reasons grounded in administrative law put forward by Dr. Healy's staff to support her decision to bypass RAC review in approving Dr. Royston's petition for expedited consideration were inadequate to sustain her disposition of the case.

Dr. Leventhal said that she had several concerns. First, that every investigator who wants to have a clinical gene therapy protocol will be asking for permission on an emergency basis. That is the nature of clinical investigators. The proposed mechanism will only be adequate if the exceptions are rare. She also expressed concern about the additional burden this will create on the staff of the ORDA. Requests for compassionate use or single patient exemptions will overwhelm the routine business of the RAC. Dr. Wivel responded that it is his understanding that these requests would be reviewed by a group of individuals. These decisions will not be confined to ORDA, but will be reviewed by Dr. Liotta and other NIH staff.

Dr. Leventhal stated that there may be factors that lead the NIH Director to grant permission for a single patient to be treated that would not bear scrutiny when a full protocol is presented. The RAC must prepare themselves for the idea that just because the committee grants approval for one patient to be treated in a particular fashion, does not necessarily assume that the multiple patient protocol will be approved by the entire RAC.

Dr. DeLeon spoke in favor of the proposed policy recommendations. If the RAC is going to review these protocols post facto after NIH approval, then a report on the outcome of the trial should be submitted to the RAC. In addition, there should be a provision that protocols that have been disapproved by the RAC should not be submitted to the NIH Director as a way of circumventing the RAC.

Dr. Krogstad requested a friendly amendment to the policy statement. An investigator will notify ORDA at the time a patient's cells are transduced, which will ultimately be used for the purpose of gene therapy. The terms compassionate use or compassionate therapy should never be used. Ms. Buc asked if she could rephrase the amendment such that when the NIH is deciding whether a protocol is truly an emergency situation, the NIH should apprise itself of circumstances (i.e., intention to transduce the patient's cells) in order to assess whether there was ample time for the normal RAC review process. Dr. Krogstad agreed to Ms. Buc's revision of the amendment. This provision would avoid the submission of an emergency request from an investigator who transduced a patient's cells as long as 4 months prior to the request.

Dr. D. Miller stated that he would not vote in favor of the proposed policy statement. The *NIH Guidelines* are entirely suitable and should be strengthened, if anything, to include a provision for expedited review. He said that he does not have faith in the limited review that would be provided by the NIH or the FDA. Safety criteria might be relaxed to such an extent that a replication competent virus will cause lymphoproliferative disease in these patients.

Dr. D. Miller stated that he sides with the Foundation on Economic Trends with regard to the necessity for public review and scrutiny. There has never been a documented cure that is attributable to gene therapy. The RAC has reversed itself 180 degrees. Because of increasing pressure to approve trials for critically ill patients, investigators will attempt to administer anything to a patient in an effort to achieve some sort of an effect. To move in this direction is bad scientific policy. Progress will be hampered instead of approving good protocols quickly.

Dr. Woodcock asked to clarify a prevailing misconception about the FDA. The FDA's safety review of these protocols, like other investigational biologics, is extremely rigorous and includes a very detailed safety assessment of the cell line used to produce these products, the potential for adventitious agents

contaminating the products, and any other safety risks that might occur. The FDA's safety evaluation is the same whether the protocol is intended for 1 or 100 patients.

Dr. Leventhal stated that due to the increasing number of human gene therapy protocols that are being submitted for RAC review, the committee might have to increase the number of meetings per year. She stated that increasing the number of meetings from 4 to 6 would decrease the time between meetings from 3 months to 2 months. Increasing the number of RAC meetings per year may resolve many of the problems discussed today.

Dr. Walters called on Dr. Wivel to summarize the proposed policy recommendation, including the amendments that were offered by the RAC members. Dr.Wivel outlined the policy statement as follows:

1. At the very outset, the RAC will make it clear that it will entertain single patient protocols.
2. No distinction will be made between research and therapy.
3. Regardless of the method of review, the criteria must be the same for all protocols.
4. NIH will state publicly as part of this policy statement, its preference for the traditional method of review.
5. When time sensitive circumstances prevail, the NIH will perform an internal review.
6. The NIH will take into consideration, among other factors, consanguinity with previously approved protocols.
7. To the extent legally and practically possible, the NIH Director will consult with RAC members, NIH experts, and any other experts deemed appropriate to the review process.
8. The NIH will report to the RAC following its internal review.
9. This policy statement will not include the terms compassionate use or compassionate treatment.
10. A protocol that has been deferred by the RAC in its normal review process will not be eligible for expedited review unless it is significantly altered from the original submission.
11. IRB and IBC approval are required prior to making a time-sensitive request from gene therapy to the NIH Director.
12. Any investigator who receives such an approval must report back to the RAC the results of the treatment.

The motion to approve this policy statement for recommendation to the NIH Director was approved by a vote of 9 in favor, 3 opposed, and 1 abstentions.

Adjournment/Dr. Walters

Dr. Walters Adjourned the special meeting of the RAC at 3:52 p.m. on January 14, 1993.

Nelson A. Wivel, M.D.
Executive Secretary

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

Date: 1/14/93

LeRoy B. Walters, Ph.D.
Chair
Recombinant DNA Advisory Committee
National Institutes of Health