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

July 31, 1990

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The Recombinant DNA Advisory Committee (RAC) was convened for its forty-fourth meeting at 9:00 a.m. on July 31, 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:

Ronald M. Atlas Charles J. Epstein Barbara E. Murray
Michael Brewer Martin F. Gellert Robert F. Murray
Ira H. Carmen Donald J. Krogstad Leonard E. Post
Donald C. Carner Brian F. Mannix Monica Riley
James F. Childress Gerard J. McGarrity Moselio Schaechter
Don B. Clewell R. Scott McIvor Nelson A. Wivel
Anna C. Epps Richard C. Mulligan (Executive Secretary)

A committee roster is attached (Attachment).

Ad hoc consultant:

Robertson Parkman, Children's Hospital of Los Angeles
LeRoy Walters, Kennedy Institute of Ethics

Liaison representative:

Daniel P. Jones, National Endowment for the Humanities

Non-voting agency representatives:

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

National Institutes of Health staff:

W. French Anderson, NHLBI
Florence Antoine, NCI
Sheri Bernstein, NHLBI
R. Michael Blaese, NCI
Monica Calderon, NCI
Barrie Carter, NIDDKD
Michelle Carter, CC
Russell Connor, CC
Kenneth Culver, NCI
Carole Graves, NCI
Christine Ireland, OD
Attan Kasid, NCI

Becky Lawson, OD
Robert Lee, NCI
Jennifer Lewis, CC
Richard Morgan, NHLBI
Heather Muster, NCI
Jeff Paterson, NCI
Bill Polvino, NHLBI
Lilly Portilla, NHLBI
Steven A. Rosenberg, NCI
Teresa Stathas, CC
Carolyn Tolstoshev, NLM
Dan Wegner, NCI

Others:

Natalie Angier, New York Times
Kenneth H. Bacon, Wall Street Journal
M. James Barrett, Genetic Therapy, Inc.
Stu Borman, American Chemical Society
Marilyn M. Chase, Wall Street Journal
Yawen Chiang, Genetic Therapy, Inc.
Marlene Cimons, LA Times
Robert Cooke, Newsday
Thomas L. Copmann, Pharmaceutical Manufacturers Association
Carol Ezzell, BioWorld
Cyril Gay
Pete Gorner, Chicago Tribune
Keith Haglund, Medical Tribune
John Irvine, University of Maryland, College Park
Tsutomu Iwakiri, The Asahi Shimbun Newspaper
Dorothy S. Jessop, Department of Agriculture
Kathy Johnson, Foundation on Economic Trends
Chris Joyce, New Scientist
Marty Katz, New York Times
Michael Kriegler, Cetus Corporation
Brian Maiorella, Cetus Corporation

Jim Martin, ABC News, 20/20
Rich McManus, NIH Record
Robert C. Moen, Genetic Therapy, Inc.
Thomas D. Palella, University of Michigan Medical Center
Fran Pollner, Medical World News
Paul Recer, Associated Press
Nan Richards, ABC News, 20/20
Jed M. Rifkin, PSI International, Inc.
Cary Ruscus, Blue Sheet
Iwa Kiri Sakaue, The Asahi Shimbun Newspaper
Clarence E. Styron, Monsanto Company
David Wheeler, Chronicle of Higher Education

ATTACHMENT B:
Excerpts from the June 1, 1990, Human Gene Therapy Subcommittee on the Presentation and Discussion of Proposed Addition to Appendix D of the *NIH Guidelines* (Human Gene Therapy Clinical Protocol -- Adenosine Deaminase Deficiency)

ATTACHMENT C:

Excepts from the July 30, 1990, Human Gene Therapy Subcommittee on the Proposed Additions to Appendix D of the *NIH Guidelines* Regarding Human Gene Therapy Protocols entitled "Treatment of Severe Combined Immunodeficiency Disease (SCID) Due to Adenosine Deaminase (ADA) Deficiency with Autologous Lymphocytes Transduced with a Human ADA Gene" and entitled "Gene Therapy of Patients with Advanced Cancer using Tumor Infiltrating Lymphocytes Transduced with the Gene Coding for Tumor Necrosis Factor"

ATTACHMENT D:

Excerpts From the July 30, 1990, Human Gene Therapy Subcommittee on the Proposed Addition to Appendix D of the *NIH Guidelines* Regarding Human Gene Transfer Clinical Protocol entitled "Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and Relapse of Malignant Disease Following Autologous Bone Marrow Transplantation"

I. CALL TO ORDER AND OPENING REMARKS:

Dr. Gerard G. McGarrity (Chair) called the meeting of the Recombinant DNA Advisory Committee (RAC) to order at 9:00 a.m., on July 31, 1990. He said a notice of the meeting had been published in the *Federal Register* on June 27, 1990, and that a quorum was present. He noted that the RAC is advisory to the Director of the National Institutes of Health and that times as published on the agenda were tentative. He called attention to the fact that Dr. Charles Epstein was attending his last meeting as a member of the RAC and thanked him for his contributions over the past 4 years.

Dr. McGarrity then welcomed the following new members to the RAC: Dr. Ira Carmen from the Departmen of Political Science, University of Illinois; Dr. Anna Epps, Associate Dean for Student Services at Tulane University School of Medicine; Dr. Donald Krogstad, Departments of Medicine and Pathology, Washington University School of Medicine, St. Louis; and Dr. Leonard Post, Director of Molecular Biology Research at the Upjohn Company, Kalamazoo, Michigan. He noted that Dr. Susan Hirano of the Department of Plant Pathology at the University of Wisconsin had also been selected as a new member, but due to a scheduling conflict, was unable to attend the meeting.

Dr. McGarrity welcomed Dr. LeRoy Walters, Chair of the Human Gene Therapy Subcommittee (HGTS), and Dr. Robertson Parkman, a member of the Human Gene Therapy Subcommittee, as *ad hoc* consultants for this meeting of the RAC.

Dr. McGarrity noted the following changes to the agenda. Item VII would not be considered because local review was incomplete. Item VIII was not submitted in time for inclusion in the *Federal Register* notice; therefore, no official vote could be taken on this matter although discussion could occur. Further, the protocol listed as Item VI was deferred by the HGTS and a summary of their actions would be presented.

Dr. McGarrity noted that the monograph *Gene Therapy for Human Patients* has now been published and is available to the general public. It is a useful guide to explaining human gene therapy to a lay audience.

He noted that there are additional copies of this monograph available for anyone who wishes to have them.

Dr. McGarrity noted that the HGTS had met on July 30, 1990, and he thanked Dr. Walters and the members for doing a truly outstanding job. He said he had been involved in the formulation of review for human gene therapy for the last 5-6 years and that during this time the "Points to Consider for Protocols for the Transfer of Recombinant DNA into the Genome of Human Subjects" document has proven itself to be a good working document. Since this document has proved flexible enough to evolve with the conditions in this area of clinical research, it has a real usefulness.

He noted the importance of an effective and timely review to the field while assuring that research in this area is as safe as is humanly possible. He noted the correlation between the reviews of this new technology with that of early research with *E. coli* where the knowledge base was very limited and no one knew the major problems. However, he said he felt the RAC and the HGTS had responded admirably to assure more timely review of protocols, while maintaining a high standard for a very strong, sound, scientific review of these protocols. He said that he felt the RAC and the HGTS had served the NIH and the general public well. He hoped that the patients undergoing this therapy would stand a better chance for success in their therapies due to these deliberations.

Dr. McGarrity noted that some future decisions as to scheduling of meetings of both the RAC and the HGTS must be made, as well as improving the efficiency of the review and its responsiveness to the investigators. Furthermore, he said decisions needed to be made relative to interactions with local Institutional Review Boards (IRBs) and Institutional Biosafety Committees (IBCs) to alleviate the necessity for the RAC and HGTS to perform work which should be done at the local level. Furthermore, he added that the issue of timetables for submissions to the RAC and HGTS must be addressed immediately.

Dr. McGarrity called the members' attention to the regional public hearings that are to take place over the next two months. He stressed that these would be an excellent mechanism to discuss the issue of interaction with local IRBs and IBCs as well as timetables for submission and urged members of the RAC to attend these meetings. He also asked members to communicate any suggestions in these areas with the Office of Recombinant DNA Activities (ORDA). He once again thanked the RAC and the HGTS for their concern and thorough scientific review of protocols in this field and asked Dr. Riley to take up the matter of the review of the minutes of the March 30, 1990, meeting of the RAC.

II. MINUTES OF THE MARCH 30, 1990 MEETING OF THE RAC:

Dr. Riley said she had read the minutes and that they conformed to her memory of the meeting with one exception. She said that under "Other Business," she felt there was confusion between the two topics of human gene therapy and the scheduling of the public hearings. She suggested moving the first sentence of the section under "Other Business" to the beginning of paragraph four. The first sentence of the first paragraph should introduce the topic of the public hearings and make it clear that the first three paragraphs have to do with the public meetings, with the following text pertaining to human gene therapy.

Dr. Riley moved adoption of the minutes with this correction.

Mr. Mannix said he also had read the minutes and agreed with Dr. Riley's suggestion for a change in wording, and he seconded the motion.

Dr. McGarrity offered a friendly amendment in the form of a request to have ORDA staff research the vote on a motion found on page 14 of the minutes. Currently the minutes reflect that the vote was "passed by

majority vote." He asked that the actual tally of votes be inserted at this point. Dr. Riley accepted this as a friendly amendment.

There being no further discussion on the motion, Dr. McGarrity called for a vote on the motion. The motion passed by a vote of 15 in favor, none opposed, and 2 abstentions.

Dr. McGarrity said, before getting into the discussion of the SCID-adenosine deaminase (ADA) deficiency protocol, that he felt it was important for members of the RAC who did not attend the meeting of the HGTS to get a flavor of what had been presented and discussed. He expressed a desire that ORDA include the appropriate portion of the minutes of the HGTS meetings of June 1 (Attachment B) and July 30, 1990, into the minutes of this meeting (See Attachment B & C). Furthermore, he said the same should be done with discussions of the proposal for human gene therapy involving the proposed use of tumor necrosis factor (TNF). He then called upon Dr. Gellert to discuss the SCID-ADA protocol.

III. PRESENTATION AND DISCUSSION OF PROPOSED ADDITION TO APPENDIX D OF THE " NIH GUIDELINES" REGARDING HUMAN GENE THERAPY PROTOCOL ENTITLED "TREATMENT OF SEVERE COMBINED IMMUNE DEFICIENCY (SCID) DUE TO ADENOSINE DEAMINASE (ADA) DEFICIENCY WITH AUTOLOGOUS LYMPHOCYTES TRANSDUCED WITH A HUMAN ADA GENE."

Dr. Gellert noted that the HGTS had discussed this protocol at both the June 1, 1990, and July 30, 1990, meetings. At the June 1, 1990, meeting, the protocol had been tentatively approved subject to the following provisos:

1. That the consent form be revised, reviewed, and accepted by the RAC at its next meeting;

Dr. Gellert noted that a revised consent form had been presented to the HGTS at the July 30, 1990, meeting and that Dr. Childress would address suggested further revisions to this form.

2. That a stronger warning with regard to the potential for malignancy be inserted into the consent form;

Dr. Gellert said this had been done.

3. That a "stop criterion" of two therapy-related deaths be inserted into the protocol;

Dr. Gellert said this had been done.

4. "That intraperitoneal infusions not be utilized without further approval by this committee;

Dr. Gellert said this was considered a hazardous procedure especially in immune deficient children. However, it had been decided by the HGTS that this could be viewed as a minor modification to the protocol if the proposed procedure for handling minor modifications to protocols were approved by the RAC.

5. That proceeding to Phase 2B of the protocol would require approval by the IRB;

Dr. Gellert said this has been agreed to by the members of the HGTS.

6. That full data from the Milan experiments of Dr. Claudio Bordignon be provided for review by the subcommittee prior to a meeting of the RAC;

Dr. Gellert said he would return to this topic for more discussion shortly.

7. That a final version of the inclusion/exclusion criteria for patients to be accepted or not accepted into the protocol reflect items such as age and length of time on Polyethylene Glycol (PEG)-ADA;

Dr. Gellert said this information had been provided on pages 51 and 52 of the revised protocol and is included as handwritten notes on those pages.

8. And that a specific plan for follow-up evaluation of the immunologic and clinical status of the patients be given.

Dr. Gellert noted that this had been inserted on pages 61 and 62 of the revised protocol.

Dr. Gellert said the only two issues to consider were the consent form and the data from the Milan experiments. He noted that Dr. Bordignon had made a presentation to the HGTS on July 30, 1990. He said Dr. Parkman could also discuss this, but Dr. Gellert made the following comments relative to this presentation.

Dr. Gellert said Dr. Bordignon's data showed that infusion of cells from a child with ADA deficiency into immunodeficient mice would be unsuccessful if the cells were not treated. However, if a vector carrying the ADA gene were inserted into the human ADA deficient cells, the cells would survive in a relatively equivalent fashion to immune cells from a normal patient. However, if a patient has been previously immunized with tetanus toxoid, then among the ADA-containing cells, one can detect a tetanus toxoid response, after passage through the mouse. He said the problems with this model were twofold. One, the cells came from a patient who had been on PEG-ADA therapy, and who would have been too well from the standpoint of immune reconstitution to be eligible for the proposed protocol. Two, the ADA-containing vector was not the same one that is being proposed in the protocol. Therefore, there are two possible models proposed for how this therapy might work:

1. ADA-containing lymphocytes may survive longer; or

2. ADA-containing cells may detoxify the environment to make the endogenous immune system in the patient function in a more normal fashion.

Dr. Gellert noted that the Milan data supports the first hypothesis but sheds no light on the second. However, despite these imperfections in the preclinical model, the HGTS felt this was promising enough evidence to vote in favor of the proposed protocol.

Dr. McGarrity called on Dr. Childress for his comments. Dr. Childress said he would elaborate on the discussion of the consent form. He said the discussion centered on the need for a stronger warning about risks of malignancy and other unknown risks. He said the revised consent and assent forms were an improvement. He stressed the helpfulness of the organization, the addition of headings, and appropriate expansion and clarity of writing in the new forms. Additional specific changes were recommended, mainly for clarification, and he said he would be happy to reply to questions about these.

Dr. Childress said suggestions from Ms. Meyers and Dr. Leventhal were received, mainly having to do with making it clear that parents are informed accurately about what will be covered in later phases of the treatment, particularly if there is movement to another treatment or to treatment outside the NIH. He said the investigators had agreed to take account of these suggestions and to revise the consent and assent

forms in response to these concerns. Dr. Childress thanked the investigators for their cooperation in making the protocol and consent forms responsive to the concerns of the subcommittee.

Dr. McIvor said that the major considerations during discussions of this protocol had centered on the mechanism by which the gene insertion was to act to lead to alleviate the symptoms, the matter of extended survival of lymphocytes containing ADA, and intracellular expression of ADA in the lymphoid cells, leading to endogenous detoxification of the environment to make the immune system function. He emphasized that the anticipated mechanism of action involves the intracellular expression of ADA in lymphocytes, leading to their increased survival.

Dr. Parkman said that there were three hypotheses which were discussed:

1. Introduction of the normal gene would allow the cells to function betterimmunologically, regardless of survival;

2. Introduction of the gene would allow the cells to live longer without changing total body tissues or changing the intrinsic capacity of the cell to mediate any degree of function; and

3. This nucleated cell, by having ADA contained within it, would do a more efficient job of reducing total body burden of deoxyadenosine. Since the toxic effects of the lack of ADA occur very early inthymic development, reducing total body burden would allow normal differentiation to occur more rapidly.

Dr. Parkman said it was important to realize that what was shown in the Milan data in amurine model had verified the results of previous *in vitro* studies performed by the NIH investigators. They demonstrated that insertion of the gene allowed the cells to live longer.

Therefore, a major consideration arises. In order for this protocol to be successful, one has to assume tha a patient who does not respond well to PEG-ADA still possesses a small number of cells capable of protective immunity. Normally these cells would die off rapidly, but by the use of gene therapy, such cells may accumulate in time, resulting in protection of the patient and improvement in his/her immune function. Furthermore, since most SCID patients do not live beyond the age of one year, the patients to be accessed into the study already are a subset of patients with a relatively mild form of this disease. Since they have survived for this long, they may benefit more readily than patients with more severe forms of the disease.

Dr. Riley said she wanted to be sure that efficacy of the treatment could be measured in patients who were already on PEG-ADA. Dr. Parkman said that the patients who would be included in the protocol would not have effective protective immunity. Despite being able to respond to a single antigen, their T cells are non-functional. He said this is proved by the need to continue to treat them with intravenous immunoglobulin. Therefore, improvements in specific immunity to antigens would be one of the proofs tha the therapy is working.

Dr. Atlas asked whether cellular treatment would be decreased if the patients developed an adequate immune response. Dr. Parkman said the protocol did not address this issue specifically but that such a reduction would be a logical next step if an improvement in specific immunologic function is demonstrated. Dr. Atlas questioned whether such a reduction in therapy would have to be brought back to the HGTS and the RAC for approval.

Dr. McGarrity said this would be a modification to the protocol and would have to be approved. However, he added that the RAC was going to consider a proposed addition to the "Points to Consider" which

would expedite minor modifications to approved protocols and would be discussed later in the meeting. If such a reduction were considered to be a minor modification, and if the RAC approved the amendment to the "Points to Consider," then a minor modification could be reviewed by the local IBC and IRB. Then the Chair of the HGTS and the Chair of the RAC could approve such a modification. Dr. Miller added that the Food and Drug Administration (FDA) would also have to approve any such changes to the protocol.

Dr. Atlas asked how many patients were likely to be eligible for the protocol and whether there were enough to draw a distinction between the existing PEG-ADA therapy and the new gene therapy. Dr. Parkman said the current pool of patients on PEG-ADA therapy was very heterogeneous in its responses to PEG-ADA, with about a third responding well, a third with partial responses, and a third who do not respond. He expected the results of the gene therapy protocol to be the same, noting that it might not work in all patients. Currently, the investigators have approximately a half dozen eligible patients who are interested in participating in the protocol. Dr. Blaese said that he felt there would be enough patients, who would fulfill the inclusion criteria over the next 3-4 years, to accumulate the patient numbers necessary for the study.

Dr. McIvor asked Dr. Parkman if he felt the withdrawal of PEG-ADA or immunoglobulin was a "minor" modification to the protocol. Dr. Parkman said he did not think so.

Dr. Gellert moved that the protocol be approved. Dr. Childress seconded the motion. Dr. Wivel asked for clarification on the issue of intraperitoneal administration. He said the motion of the HGTS for approval of the protocol included a proviso that intraperitoneal (I.P.) administration not be carried out at this time. Dr. McGarrity asked Dr. McIvor if this was also included in his question as to what constituted a minor change in the protocol. Dr. McIvor said he was only referring to withdrawal of PEG-ADA or immunoglobulin treatment. Dr. Parkman said he remembered specifically that the HGTS had agreed that the investigators could choose to ask that the introduction of I.P. administration be viewed as a minor modification. However, the HGTS did not want to prejudge the outcome of such an application and left this up to the Chair of the RAC to decide whether he felt this would be a minor modification, dependent upon the information supplied as part of any such application.

Dr. McGarrity also noted that the current protocol, as approved, called for 10 patients to be treated and asked if an increase above this number should be viewed as a minor modification. Dr. Parkman said it would depend upon the results in those 10 patients. Dr. McGarrity said this could be taken up at a later date.

There being no further discussion, Dr. McGarrity put the motion to approve the protocol to a vote. The motion passed by a vote of 16 in favor, 1 opposed, and zero abstentions.

IV. Proposed Addition to Appendix D of the "NIH Guidelines" regarding Human Gene Therapy Protocol entitled "Gene Therapy of Patients with Advanced Cancer using Tumor Infiltrating Lymphocytes Transduced with the Gene Coding for Tumor Necrosis Factor (TNF)":

Dr. McGarrity called on Dr. McIvor to begin the discussion of this protocol. Dr. McIvor said he presented a lengthy review at the HGTS meeting, and he would summarize the major points of this review for members of the RAC who were not present at that meeting.

Dr. McIvor said the proposal presented some new challenges in terms of consideration of human gene therapy protocols. He pointed to the fact that the protocol seeks to express a biological response modifier (tumor necrosis factor) in tumor infiltrating lymphocytes (TIL), and that the mechanism of action for this protein is not well understood. Furthermore, it is known that TNF has a number of toxic effects associated

with it. Therefore, there are issues of safety that have to be considered. There is relatively minimal preclinical animal data to show the protocol is either safe or efficacious. Some *in vitro* experimentation had been done on TNF-transduced TIL, but the investigators relied primarily upon observed results in administration of TNF by infusion or injection for predicting safety and efficacy.

Dr. McIvor said that since the patients to be included in the protocol were suffering from advanced metastatic cancer, every possible consideration to move forward with the new therapy should be encouraged. He said the possibility of viral spread from TILs into other tissues was an unlikely event. However, he noted that if this occurred through some unknown mechanism, it could lead to some detrimental effects in the patients.

Dr. McIvor said the main risk involved in this therapy is the over-expression ofTNF in the body that could lead to a toxic effect. He noted toxic effects have been seen by administration ofTNF by injection and infusion at levels of 8 micrograms per kilogram per day. The protocol, however, calls for an initial level of systemic TNF expression of .07 micrograms per kilogram per day, far below the observed toxicity level previously noted. He pointed to the fact thatTNF expression as a result of infusion may be different from cellular expression, but that TIL and lymphokine activated killer (LAK) cells both express low levels of TNF and have been administered to patients in high amount without toxic effects. Therefore, Dr. McIvor felt it was unlikely that a toxic effect would be observed and that the procedure was safe.

Dr. McIvor said additional primate studies were conducted as a result of local review, and initial data indicated that infusion of TNF-transduced TILs showed no toxicity. However, he said IL-2 was not co-administered because of difficulties with IL-2 administration. Therefore, it was unlikely that a significant level of maintenance of the TILs was achieved in the monkeys. It did prove that administration of the TILTNF was not toxic.

Dr. McIvor said that if a toxic effect is observed, there are a number of options open to the investigators, namely:

1. Withdrawal of IL-2 administration;

2. Steroid administration; and

3. Administration of anti-TNF antibody.

Dr. McIvor said that it had been previously observed in preclinical and clinical studies that administration of TNF can lead to tumor regression. However, in humans the problem has been extreme toxicity; there is a need to investigate local expression of TNF at the tumor site to limit systemic toxicity. A major question is whether enough TILs will migrate to the tumor site to produce regression of the tumor. However, he said the HGTS was satisfied that the possibility of an efficacious outcome warranted approval of the study.

Finally, Dr. McIvor emphasized that the study has been termed a "Phase I" study. Therefore, the main focus of the study is to determine toxicity, not necessarily efficacy. Another study would have to be proposed later to determine actual efficacy. He said theHGTS approved this protocol on the condition that final IBC and IRB approval be granted as well as minor revisions to the informed consent document.

Dr. Clewell said the proposal is a clinical study and the results will be of great interest from the standpoint of efficacy of TNF in tumor control, as well as the potential for this type of gene therapy. He noted that Dr. Rosenberg and his colleagues have a great deal of experience in developing and testing immunotherapeutic approaches to the treatment of various malignancies. This study is a natural and

reasonable outgrowth of their previous studies with TIL cells.

Dr. Clewell said the retroviral vector system is based on ongoing TIL studies, with the main difference being the addition of a segment of recombinant cDNA coding for human TNF. He noted that the investigators had proved the vector could be successfully established by both G418 resistance testing and Southern blot analysis. Western blot analysis indicated production of additional TNF by transduced cells. Supernatants have been tested and shown not to contain active virus, and transduced TILs were shown in PCR studies to be free of viral envelope antigens. Furthermore, transduced TILs were shown to be dependent on IL-2 for growth and survival.

Dr. Clewell said several questions were raised by the NIH IRBs and the IBC, and that these committees had asked for:

1. Primate toxicity studies;

2. Studies using murine neutralizing antibody to human TNF in mouse experiments; and

3. A review of further data from the N2-TIL trafficking experiments, including available autopsy data.

Dr. Clewell said these were addressed in an addendum to the protocol dated May 24, 1990. Dr. Rosenberg addressed all of these points, as well as other points relating to toxicity, at the meeting of the HGTS which took place on July 30. The main issues were:

1. That the investigators relied on estimates of TNF expression based on production by TIL TNF *in vitro*, and that levels of expression may differ via cellular expression *in vivo*; and

2. That while transduced TILs are dependent on the addition of IL-2 in culture, this level of dependence is not clear *in vivo*, and therefore may be important in considering IL-2 withdrawal as a means of reversing TNF toxicity.

Dr. Clewell said that, despite the drawback of not having a good animal model, he supported the proposal with some enthusiasm. The information to be gained from the studies seemed to justify the possible risks in light of the clinical status of the patients in whom the studies would be conducted.

Dr. Epstein said he wanted to return to the issue of the consent form since he had made the motion at the HGTS meeting and that one of the contingencies to the motion was that the consent form be revised.

Dr. Epstein said there was a lengthy semantic discussion of what constituted a Phase I trial. Since a Phase I trial is to determine toxicity and maximum tolerated doses independent of efficacy, efficacy was not an issue in the approval of the protocol. However, in the discussion by the HGTS, it was pointed out that the consent form was not proper for a Phase I trial and that Dr. McCarthy had made an impassioned request that the form be revised appropriately. Dr. Epstein said that, despite attempts at revision overnight by the investigators, the form still was not appropriate to a Phase I study.

Dr. Epstein said the title of the study is "Gene Therapy of Patients with Advanced Cancer Using Tumor Infiltrating Lymphocytes Transduced with the Gene Coding for Tumor Necrosis Factor." Nowhere in the title does it reflect that it is a Phase I toxicity study. He said a better title would be, "Ascertainment of the Maximum Dose of Tumor Infiltrating Lymphocytes Transduced with the Gene Coding for Tumor Necrosis Factor That Can Be Administered to Patients with Advanced Cancer." Further, the form contains many references to "treatments." A scientifically naive person would sign this form thinking that the purpose of

the study is to treat his or her cancer.

Dr. Rosenberg said he tried to incorporate the sense of what was discussed in the HGTS, and he was willing to make additional changes. He did add a sentence in the second paragraph of the form to illustrate that the purpose of the study was to determine the maximum tolerable dose of the TILTNF, and it is not predictable at this time whether the insertion of the gene will have any benefit to the patient. Furthermore, the patients are currently getting a treatment (IL-2 administration) which has been used for almost two and a half years and which has benefited some patients. The addition of the gene insertion was intended to be seen as the portion of the treatment for which it was impossible, at this time, to predict benefit to the patient.

Dr. Parkman said that the patients were receiving two treatments (IL-2 therapy and TIL therapy) in one, and that one way to address this would be to have them sign separate consent forms. He said the issue of toxicity is not spelled out in the consent form, as well as options for therapies that may have to be instituted to reverse the toxicity if it occurs. Since this protocol is going to result in toxicity in some patients in order to find the maximum tolerated dose, the side effects of TNF toxicity should be pointed out, and a separate consent form should be signed.

Dr. Walters said he supported Dr. Parkman's comments. He thought the choice should be made clear to patients as to whether to continue with an existing and apparently successful protocol or to consent to participation in a Phase I study with tumor necrosis factor.

Dr. Miller said that while he agreed with Dr. Parkman's presentation, it did not seem correct to subject the patients to signing two consent forms because this study is indeed separate from the standard TIL cell therapy. To include a TIL cell therapy consent form and a TILTNF therapy consent form is not appropriate.

Dr. B. Murray asked if patients who did not elect to enter the TILTNF protocol would still be eligible for IL-2/TIL cell therapy. Dr. Rosenberg said that was correct, and that there are a larger number of patients with advanced melanoma seeking care than can possibly be treated. Patients who do not elect to enter the protocol would be offered a different protocol. Dr. B. Murray said she agreed with Dr. Epstein that the consent form implies they would be getting an efficacious treatment and could be viewed as an enticement.

Dr. McGarrity asked if patients selected for the TNF study would necessarily be getting TIL/IL-2. Dr. Rosenberg said it was not necessarily the case.

Dr. Atlas said he thought the protocol bridges both Phase I and Phase II clinical studies. He said that each patient is his own control. If the patient can reach a maximally tolerated dose, the treatment may work for that patient and he suggested telling the patient, "You're actually going to go through a treatment. If you tolerate the dose that we're trying to achieve, you survive long enough, and it works, you have some hope."

Dr. Miller said this was a simplistic view. In fact, the expectation of efficacy is very low, but that this study will help elucidate starting dose and frequency of infusion necessary to test efficacy. Furthermore, it may only work in a subset of patients, and this will be important to know.

Dr. McGarrity asked whether the consensus of the group was that two consent forms were needed or whether separate wording or separate paragraphs for the TIL/IL-2 and TILTNF was needed.

Dr. Parkman said the protocol, as written, did not focus enough on the issue of potential toxicity, the

over-expression of TNF, and methods for ameliorating this toxicity should it occur. He said it was irrelevant whether this was done in one document or two, but that the risks and benefits of both needed to be addressed. He said this currently was a good consent document for TIL/IL-2, but not for a Phase I study of TNF toxicity.

Dr. Mulligan said that one solution would be to make a third section in the protocol to discuss the TNF with a separate heading, similar to the discussion of TIL and IL-2 as found on pages 2 and 3 of the consent document.

Dr. Childress said he had more problems with the wording of the first paragraph and suggested that a revised consent form be reviewed by two or three members of the RAC. Dr. Rosenberg said he wanted to have a consent form that the group felt was satisfactory, and he was willing to work with members of the RAC to ensure this.

Dr. McGarrity suggested that Drs. Rosenberg, Walters, Parkman, and Epstein confer during the coffee break, bring back to the group an outline of topics that would make the committee more comfortable, and have the consent form come back before the RAC at a future date.

After the coffee break, Dr. McGarrity said that some work had been done on the consent form. He asked Dr. Epstein to summarize what had been accomplished.

Dr. Epstein said that the group had specific wording worked out as to the first couple of paragraphs of the consent document. This incorporated all the concerns that were expressed, as well as additional changes to be made in the organization to include TNF toxicity. He said the group was satisfied with what had been developed.

Dr. Walters said the language that was drafted states the purpose of the TNF element of the current study clearly, and the group agreed that it would be wise to break this out as a separate section in the consent form, resulting in separate sections for IL-2, TIL cells, and TNF.

Dr. McGarrity asked for other comments on the consent document. There being no further comment, he asked for questions or comments on the remainder of the protocol.

Dr. Schaechter said he wished to see more discussion of the issue of safety. In particular, he wanted to hear more detail on the question of what can be expected from the introduction of genetically modified cells in terms of over expression and the ability to intervene with removal of IL-2, as well as treatment with steroids and antibodies to shut down over-production of a toxic dose of TNF.

Dr. McIvor once again stressed that the predictions of safety were based on *in vitro* experiments, and there may be a difference in level of expression *in vivo*, which could lead to an enhanced toxic effect. The only way to determine whether this will occur is to perform the experiments *in vivo*. Furthermore, the only *in vivo* data was provided from a study in monkeys in which IL-2 was not co-administered. Therefore, such data is not totally analogous to the study being proposed. Some questions do exist about the potential for a toxic effect in this protocol.

Dr. Rosenberg said that there are four lines of evidence that support the selection of the starting dose:

1. The starting dose of cells to be used produces less than 1 percent of the TNF per day tolerated by humans following intravenous infusion;

2. Up to 6 X 10 TIL, which make TNF in low amounts, have been given to human patients and the total amount of TNF made by those cells is in substantial excess to that of the starting dose proposed of TILTNF;

3. LAK cells have been given to almost 200 patients now. These cells make substantial amounts of TNF (500 picograms per 10 cells per 24 hours) and they are cleared in a method similar to that of TILTNF; and

4. Monkey studies have been performed to control for the initial toxicity of giving the cells.

Dr. Schaechter asked for more information on ameliorating toxicity with removal of IL-2, administration of steroids, and use of anti-TNF antibody.

Dr. Rosenberg said that over 800 patients had been treated with high dose IL-2, with or without cells. In every case when IL-2 is removed, the side effects dissipate. The cells are checked beforehand to ensure they die in the absence of IL-2, and they would not be given to a patient if this were not the case.

Secondly, Dr. Rosenberg said if there is severe toxicity due to the TNF, 4 milligrams of dexamethasone will be administered every 6 hours for 48 hours. This has a substantial antilymphocyte effect in man and should remove almost all detectable lymphocytes. Furthermore, in conjunction with cessation of IL-2, it should be very effective in ameliorating toxicity.

Thirdly, Dr. Rosenberg said his group is working hard to obtain anti-TNF antibodies. These have been shown in non-human primates to abrogate the effects of endotoxemia which leads to TNF production. He said anti-TNF antibodies are not commercially available at the present time but that Cetus Corporation is working on one that could be used in humans. Dr. Rosenberg's group is working closely with them to ensure its availability should the need arise. It would require FDA approval before use.

Dr. R. Murray asked if there were a precedent to believe that *in vivo* expression of a particular element in cells might surpass *in vitro* expression, or whether this was purely hypothetical.
Dr. Rosenberg said such a phenomenon had not been seen with TIL. In fact, the opposite seems to be true, that *in vivo* they die more quickly and are cleared. Dr. Anderson reiterated this point and said that the real problem would relate more to efficacy rather than safety due to the rapid clearance *in vivo*.

Dr. Krogstad asked what was the amount of antibody needed to neutralize biological effects of the TNF toxicity and how that compares to how much is currently available. Dr. Rosenberg said anti-TNF antibody is not available yet, but realistically he felt enough could be made available to do the job.

Mr. Brewer asked what effect the withdrawal of IL-2 in the case of TNF toxicity would have on the underlying TIL therapy. Dr. Rosenberg said any premature withdrawal of IL-2 will lead to decreased efficacy of the TIL, therefore, the efficacy of the treatment will be decreased. Mr. Brewer asked if there was any additional risk to the patient from withdrawal of the experimental therapy. Dr. Rosenberg said he knew of none except the potential progression of their underlying cancer. Dr. Schaechter reminded the group that although there are three potentially effective modalities for decreasing toxicity, they cannot be used without a price.

Dr. Epstein moved that:

"We approve this protocol with the final consent form to be reviewed administratively to see that it is consistent with the discussion, and pending local IBC approval."

Mr. Brewer seconded the motion.

There being no further discussion on the motion, Dr. McGarrity put it to a vote. The motion passed by a vote of 17 in favor, 0 opposed, and no abstentions.

Dr. McGarrity thanked the committee and said he felt it worthwhile to reflect on the significance of the two motions passed during the morning session. They are the first approvals for true gene therapy rather than simple gene insertion. He noted that this is a historic occasion in that now gene therapy can be added to the repertoire of vaccines, antibiotics, drugs, surgery, and radiation to fight disease.

Dr. McGarrity thanked the members of the RAC, the members of the HGTS, and the HGTS Chair--Dr. Walters. In his opinion, the public and national purpose had been well served by the debate and discussion. He thanked the investigators for their help and cooperation and wished them luck in the execution of these protocols. He especially thanked Dr. W. French Anderson who he said had "pioneered and taken this from a very embryonic stage four or five years ago."

Dr. Anderson noted the rigor of the review but said it had been very fair and very thorough. The public should be comfortable with the intense review process that had taken place. He expressed the investigators' appreciation for the timeliness of the review and the effort that had been put into it.

Dr. Parkman noted that at the meeting of the HGTS, Dr. Claudio Bordignon, who presented the data on his experiments in Milan, had made the observation that, in Italy, none of the processes that were being undertaken by the RAC and the HGTS would be required. He could choose to proceed to this type of clinical experimentation without review, but he did not feel he was scientifically ready at this point. Further, Dr. Bordignon had said he was pleased to take part in the process and he felt the process was a good one.

V. Presentation and Discussion of Proposed Addition to the "Points to Consider" Document to Expedite Minor Modification on Approved Protocols:

Dr. McGarrity called on Dr. R. Murray to begin the discussion of this agenda item. Dr. R. Murray said the rationale behind the proposed change to the "Points to Consider" document was to allow for investigators to make minor modifications or changes in their protocols without having to wait for the next meeting of the RAC or the HGTS. He said the first paragraph of the proposed addition was developed by Dr. Areen and reads as follows:

"A minor change in protocols approved by the Human Gene Therapy Subcommittee and the RAC is a change that does not significantly alter the basic design of a protocol and that does not increase risk to the subjects. If the change has been approved by the relevant Institutional Review Board and Institutional Biosafety Committee and the Chair of the Human Gene Therapy Subcommittee, the Chair of the RAC may then give approval. The Chairs will report on any such approvals at the next regularly scheduled meetings of the respective committees."

Dr. R. Murray suggested that a sentence be added before the sentence beginning, "The Chairs will report...." which would read as follows:

"The Chair of either committee may consult with one or more other committee members, if deemed necessary."

Dr. R. Murray said this may not be self-evident and that he was sure the current Chairs would be doing

this in any event, but that for future Chairs who may not have the same "democratic outlook" he suggested this sentence be inserted.

Dr. McGarrity said he was completely comfortable with this and would support the inclusion of the additional sentence.

Mr. Brewer said this proposed addition was developed to address the problem that, without such language, all changes would have to go through the entire process. With the limited number of meetings each year there was concern that unnecessary delay and interruption in experimental procedures would result. Although the primary purpose of the RAC and the HGTS is to ensure public health and safety with regard to aspects of recombinant DNA research and human gene therapy research, the committees should eliminate any barriers to research in progress. There is a belief that minor changes in a protocol need not go through the complete review.

Mr. Brewer said it is important to understand that there are two judgments which the committees are delegating to the Chairs:

1. To determine if the change is minor or major; and,

2. If the change is deemed to be minor, whether it should be approved.

Mr. Brewer said this provides sufficient latitude for the Chairs to exercise judgment and not simply be a "rubber stamp." Further, it gives the investigators the flexibility of going to the Chairs with a proposal for a minor change, thus streamlining the process for continuing their research without going through the entire process of HGTS approval and RAC approval.

Further, Mr. Brewer said he did not believe this contradicted an interpretation of the "Points to Consider" made on December 9, 1988, that, "the substitution of a vector with superior properties is within the accepted flexibility of a protocol which is inherent within the definition and approval of an existing protocol." He said this should be clarified one way or the other. He noted that it was subject to FDA approval and RAC notification.

Mr. Brewer also said the wording in discussion of risk needed to be looked at and suggested that the phrase "...does not unreasonably increase risk...." be added to the first sentence to allow the Chair some latitude in determining what is a minor modification as regards risk to the patient.

Dr. Parkman said he felt that as an IRB Chair, most Chairs tend to be conservative when utilizing such a procedure. If there were any significant questions, most Chairs would tend to bring the issue to the full forum.

Dr. McGarrity said he felt he would not be making any decisions unilaterally, but rather he would confer with members of the committee or the subcommittee before making a decision on whether any issue was a major or minor modification.

Dr. Rosenberg said he felt the proposed change was an excellent one, but that it raised another possible issue for consideration. He said that most committees that consider clinical protocols meet biweekly or monthly. Now that the HGTS is considering clinical protocols it is a problem for them as well as the RAC to meet only once every four months. He said a four month delay on a theoretical issue was one thing. However, in the clinical area this is not acceptable in light of even major modifications which may have to be examined expeditiously if a new development occurs which may bring some benefit to patients.

Dr. McGarrity said he agreed and said the committee was sensitive to this issue. He said the HGTS had discussed this issue and was unable to come up with clear-cut answers as far as efficient and timely review of protocols. Further, Dr. McGarrity expressed concern that this problem would be exacerbated now that the initial hurdles of gene therapy had been cleared and the subcommittee could expect many more protocols coming to their attention at each meeting. He urged people to contribute concrete suggestions for dealing with these issues not only before the RAC but at the regional meetings which will take place this fall. He said it is a pressing issue which must be dealt with promptly, and he hoped some individuals or groups could assist the RAC in addressing it.

Dr. Parkman said that Dr. R. Murray brought up the question before the HGTS of what its function was, whether it was to aid researchers in the development of their proposals, or to make sure the best science was done in terms of gene therapy. He said in many cases, the protocols coming before the HGTS were not complete enough to be instituted, if approved, and were merely "think pieces" looking for feedback from the HGTS. He said the application from St. Jude's was a case in point. Even if the HGTS had approved it, the investigators were not ready to institute the protocol. He asked if the HGTS was going to continue to be a sounding board for investigators outside the NIH or whether there should be criteria set up for all proposals coming before it. There should be finished protocols which have been approved by local review boards with regard to all other scientific, ethical, and IRB issues before they can be submitted to the HGTS.

Dr. Parkman said he felt the committees have a dual function at present. He did not want to deprive non-NIH investigators of the same kind of benefits which have been afforded to the NIH scientists, but at the same time the pressures of increased workload may not permit the HGTS and the RAC to perform this function.

Dr. Post asked if it was the intent of this proposed change to the "Points to Consider" that all clinical details and modifications that did not necessarily have implications for the gene therapy portion of the procedure also had to come back through the RAC, or whether this is delegated to the IRBs and the FDA. Dr. McGarrity said he believed that protocols are approved as submitted. If any significant changes are to be made, they would have to be reviewed again. This proposed amendment is only to facilitate approval of minor modifications and changes.

Dr. Epstein said he thought that only changes that were in the purview of the RAC would have to come back before it. The local IRB may sign off on any internal things which do not need to come back before the RAC. Dr. McGarrity asked Dr. Parkman to comment on this.

Dr. Parkman said the present understanding is that if one has an approved protocol and one wishes to make a change in that protocol, i.e., the issue of intravenous versus intraperitoneal administration of cells, there should be legitimate reasons for why this change should occur. It should first go to the local IRB for approval and then be forwarded to the HGTS and the RAC. He said he viewed the protocols as being approved in total and that decisions made by the local IRB would weigh heavily on the determination of whether something was a major or minor modification.

Dr. R. Murray moved adoption of the proposed change to the "Points to Consider," as amended by himself and Mr. Brewer. Mr. Brewer said he did not want to append specific wording to the document as proposed. However, he felt it should be viewed as a "rule of construction," that the criteria should define a minor modification as one that does not knowingly and unreasonably increase risk. This would allow the Chair to have some flexibility and latitude and not be bound by precise language which cannot be met. Mr. Brewer seconded Dr. R. Murray's motion.

Dr. Post asked a procedural question. Since the RAC's function is advisory in nature to the Director of NIH, do these kinds of changes have to go beyond the Chairs of the HGTS and the RAC for approval? Dr. Wivel said this was not the case.

Dr. Childress said he felt the wording of Dr. R. Murray's amendment to the proposed change should be changed since it is assumed that the Chairs can consult with whomever they wish. He suggested the wording of the sentence be:

"It is expected that the Chairs will consult with appropriate members of the committee."

Dr. R. Murray agreed, saying this was a diplomatic way to state the expectation of the committee in this regard, and he accepted this as a friendly amendment.

There being no further discussion, Dr. McGarrity put the motion to a vote. The motion passed by a vote of 17 in favor, 0 opposed, and no abstentions.

VI. Proposed Addition to Appendix D of the "NIH Guidelines" Regarding Human Gene Transfer Clinical Protocol entitled "Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and Relapse of Malignant Disease Following Autologous Bone Marrow Transplantation:

Dr. McGarrity said this item was deferred by the HGTS in its meeting yesterday, but asked whether Drs. Mulligan or B. Murray would like to make comments on it beyond the fact that it was deferred.

Dr. Mulligan said that this was another gene marking approach, using autologous bone marrow transplantation to ask important questions about metastatic cancer cells. In certain treatment protocols, one removes bone marrow for later reinsertion after high-dose chemotherapy. If cancer recurs in such patients, either the chemotherapy was not adequate or there were residual cancer cells in the bone marrow sample. The concept is to mark the sample by a retrovirus infection and then reconstitute it. If a relapse of the cancer occurs, it is important to know if one can or cannot detect the marked cells. If marke cells are detected, it is apparent the bone marrow sample contained residual cancer cells; if no marked cells are present, then the treatment of the patient was adequate.

Dr. Mulligan said that the concept was sound and sensible but that safety issues surrounding the manipulations of the cells *in vitro* would affect their capacity for transplantation or growth of the cancer. He said the authors did not supply any *in vitro* data as to how they were going to do the retroviral infections which was key in determining the ability of the marrow to reconstitute. The investigators were given some questions to answer and asked to submit a revised protocol based on those answers. Furthermore, there was discussion of whether the investigation should be more focused in that they proposed to study different cancers. No real consensus was reached on whether there should be separate proposals for each type of tumor. However, more *in vitro* data was required for an assessment of the protocol.

Dr. B. Murray asked if the minutes of the subcommittee meeting in reference to this would be included in those issues to be appended to the RAC minutes as Dr. McGarrity had indicated earlier. Dr. McGarrity said that since this issue was deferred, the entire discussion should remain within the subcommittee minutes. He said he meant to refer only to the ADA and TNF sections which would be incorporated in today's minutes, but that if she thought it appropriate that this could also be included. Dr. B. Murray said she felt if she were going to be a future reviewer on this protocol that she would like to see those discussions. Dr. McGarrity said the material would be included in the minutes of the meeting of the RAC

(Attachment D).

Dr. Anderson said that as an associate investigator on this grant, he was representing Dr. Brenner. He noted that all the proposals for human gene therapy to date had come from investigators inside the NIH. This represented the first attempt by an investigator outside the NIH to seek approval of a human gene therapy protocol. This could have been done in two ways. One way would have been for everything to have been polished up and worked out and had local approvals in place. However, the local IRB had been uncertain and said, "This is fine to start, as sort of a general concept, to be considered in future years." So the intent was to have the investigators go ahead and submit the protocol and see how the HGTS and the RAC respond, since they will use the same materials and many of the procedures that were used in the N2-TIL protocol.

Dr. Anderson said many other institutions are contemplating submitting protocols. However, their local committees are equally as uncomfortable about what to do with them. This is why he felt that Dr. Parkman's view that protocols be completely approved by the local review committees is inappropriate because local committees clearly need the experience of the national review, at least on initial protocols, to feel comfortable in approving them.

Dr. McGarrity noted that another disadvantage to the local IRBs and IBCs is that, in most cases, the local experts are the investigators submitting the proposal. Thus, the committees have to go off campus to obtain advice on these protocols.

Dr. Parkman said this issue goes back again to what Dr. R. Murray had said about the difference between presenting a protocol and presenting an idea. He said this points out that if the charge of the HGTS is to be the guardians of the quality of science, then it is fair to require finished protocols. However, if there is an obligation on the part of the subcommittee and the RAC to aid in the development of good science, then it may be worthwhile to have people make proposals for research, which is different than a finished protocol. He said that if the subcommittee tries to deal on both levels, it will produce extra work and must be

undertaken with a different mind set.

Dr. Anderson said that Dr. R. Murray pointed out to the subcommittee, that when it initially started, it had to cancel meetings because there were no protocols. In fact the members undertook a "practice protocol" in order to learn about protocols. Through this process the subcommittee has learned much about dealing with protocols and assessing them, whereas local review groups are still naive about this process.

Dr. Epstein said he was worried this was a luxury that could not be afforded. He noted that Dr. Rosenberg was worried that the subcommittee could not handle the volume of protocols that will be forthcoming. Now the issue is being considered to give advisory opinions to people who do not have finished protocols. He said he felt it was an issue of how the subcommittee and the RAC was going to conduct its business. He felt if a protocol is submitted, it should be reviewed as a protocol, which is a lot of work. He said that what has happened in the past has happened, but that people must be informed that they cannot tie up the subcommittee reviewing preliminary protocols which are essentially unfinished.

Dr. Anderson said he felt that in a couple of years this would indeed be impossible, but that in the initial stages it would be worthwhile to make efforts to educate the institutions. Dr. Epstein said he did not know how people could be expected to properly review a protocol that was not developed to the point where a review would be in order.

Dr. McGarrity said that possibly other forums could be used to try to get the education process started. He suggested professional meetings, symposia, and the use of the *Human Gene Therapy Journal* as possible means of doing this.

Dr. Miller said that FDA reviewers often meet with investigators long before they submit a proposal for a clinical trial and discuss three general areas: the physical-chemical characterization of the product, the supporting animal studies that need to be done, and the clinical protocol and time lines for these. This is important, especially for academic investigators, in preparing formal proposals. Further, he added that the RAC and the HGTS had been spoiled by the high quality of the applications from Drs. Anderson, Blaese, and Rosenberg and that such applications would be in the top tenth of one percent in quality, responsiveness, and comprehensiveness that he has seen. An average academic investigator could not be expected to be in that league as far as submitting a proposal, and yet he or she deserves the consultation and support to get to a stage where a protocol would have a chance for approval.

Dr. Epstein said he could understand the need for consultation, but outside of the framework of a formal meeting and *Federal Register* notification. Dr. Miller replied that a consultation could be done during a regular subcommittee meeting, or by consulting with individual members of the HGTS who are expert in certain areas. He noted that scientific experts at FDA, who are bench scientists, are also willing to consult on these issues.

Dr. McGarrity said he did not know if the committee had been spoiled by the protocols it had received thus far, but that the standard for future applications has been set for everyone else. He noted that Dr. Wivel does consult with investigators extensively and that is part of the duties of ORDA.

Dr. Parkman said he thought people go away disappointed when their expectations are not fulfilled. The committee should make it very clear that the review of a proposal is different from responses to "think pieces." He said this may lessen some of the disappointment. He said the St. Jude's proposal could have been handled much more expeditiously if this had been the case. The committee could have spent a short time letting the investigators know about the deficiencies in the protocol without having to go through educating the entire committee to the proposal and discussing it in detail.

Dr. Parkman said that the issue of the dual role (consultation and review) of the HGTS is something that needs to be looked at, but that probably it could perform this function for another year or two. Ultimately, the consultative role would have to be accomplished outside of regularly scheduled meetings. For the present, Dr. Parkman said he would like to see the subcommittee continue both these functions.

VII. Discussion on Review of Appendix K of the "NIH Guidelines":

Dr. McGarrity called on Dr. Riley to begin the discussion of this agenda item. Dr. Riley said the Industrial Biotechnology Association (IBA) and the Pharmaceutical Manufacturers Association (PMA) had proposed that Appendix K of the *NIH Guidelines* be modified to make it possible for large scale, i.e., greater than 10 liters, culture of organisms produced with recombinant DNA techniques to be dealt with at a safety level described as "good industrial large-scale practice." This class of organisms is harmless (described as non-pathogenic, non-toxigenic, not producing toxins, and in other ways considered safe). She noted that safety level had been adopted for use by the Organization for Economic Cooperation and Development (OECD), a European based international organization, for dealing with large-scale work with microorganisms.

Dr. Riley said that there was no document provided with the submission detailing exactly what were the provisions of "good industrial large-scale practices." She said they did supply a graphic illustration

comparing such practices to biological safety levels for dealing with biological hazards, and they showed the same escalation in precautions as the hazards became greater.

Dr. Riley said she felt the rationale for this submission was that the IBA and PMA thought that there was no reason to have increased precautions in dealing with large-scale production, simply because the technique used recombinant DNA. This request reflected once again the product versus process issue that the RAC has dealt with many times in the past.

Dr. Riley noted that this change would affect both industrial organizations and research using volumes greater than 10 liters. She said she had no idea how this may impact an academic situation or non-industrial research environment.

Dr. McGarrity called on Dr. Copmann of the PMA for comment. He said he felt the proposal was well presented by Dr. Riley.

Dr. Wivel asked Dr. Riley if it would be agreeable to have the Subcommittee on Modification of the *NIH Guidelines* review this before the October meeting of the RAC. Dr. Riley said she thought that was a good idea and noted that the actual stipulations of "good industrial practices" could be supplied to allow for more cogent discussion of the proposal.

Dr. Atlas asked whether, if by adopting this modification allowing for "good industrial practices," a facility performing such experiments would be termed a "contained facility" despite the fact there are no provisions in the proposal addressing non-release to the environment. He noted that there was a bill in a congressional subcommittee which seeks to regulate all deliberately modified organisms released to the environment, but this would exclude from its permit process those facilities considered under the *NIH Guidelines* to be "contained facilities."

Dr. Riley said she did not believe such a facility would be deemed a "contained facility" due to this proposed change in Appendix K, and she asked if the use of the term "modified organisms" would include mutated organisms. Dr. Atlas said that the current language of the bill would include mutated organisms including deletion mutants.

Dr. Riley said she welcomed input on this proposal from others. She felt that the bill before the Congress was not particularly rational and would have a major impact on the industry. Dr. McGarrity noted that legal advice would be given to make sure that any language used in effecting this proposed change to the *NIH Guidelines* would be consistent with this legislation as well as impact on environmental release which are addressed by the U.S. Department of Agriculture and the Environmental Protection Agency regulations.

Dr. Post said it was his understanding that the RAC had already allowed local IBCs to take certain categories of work and designate they could be done with "good industrial large-scale practices." This proposal is merely giving the local IBCs more guidance on what constitutes "good industrial large-scale practices."

Dr. McGarrity said he was not sure that what is currently in the *NIH Guidelines* would apply to effluents coming out of process fermenters. This was a major item of concern in the proposal, that effluents would have to be sterilized and gases treated coming from these closed systems. Dr. Wivel said that this is addressed by the qualification that the proposed amendment deals with non-toxigenic and non-pathogenic organisms. Dr. McGarrity said he would refer this to Dr. Riley's group for further discussion and have it brought up again at the October meeting of the RAC.

VIII. Regional Public Hearings:

Dr. McGarrity called on Dr. Wivel to discuss the regional public hearings planned for the fall. Dr. Wivel said that most preliminary materials had been distributed as well as the schedule of meetings which includes dates, times and meeting locations. He said if members of the committee desired changes in assigned meeting locations because of travel and schedule conflicts that they contact ORDA.

Dr. Wivel called the committee's attention to the draft of a background commentary on the meetings which will be sent to all interested parties, and he asked for members' comments on any changes that need to be made in this document. He said the questions which were included in the document were not meant to be inclusive and he welcomed suggestions from members of the committee. He said the last two days of meetings had resulted in an additional question which he would include in the final version of the document. This would pertain to submission and review of gene therapy protocols. He asked for comments from the committee.

Dr. Gellert said he felt the question of the use of polymerase chain reaction (PCR) as a means of generating "quasi-non-recombinant" products should be added to the list of techniques to be discussed. Dr. Wivel said he would add that to the list.

Dr. R. Murray asked if an outline or guideline had been developed for the actual conduct of the meetings. Dr. Wivel said it would be very simple. He said Dr. McGarrity had volunteered to attend all the meetings. The meetings would include a brief introductory statement by Dr. McGarrity as well as representatives of the host institutions, and the remainder of the day will be devoted to hearing testimony from people wishing to present their views. The formal portion of the meetings will be kept to a minimum, allowing maximum time for public participation.

Dr. Wivel noted that ORDA has requested a one-page summary of testimony from all public participants who pre-register to testify, and those people will receive a priority in testifying over people who simply may walk in and wish to testify. Dr. Wivel said it is intended that each speaker be given 5 minutes to make his or her presentation.

Dr. R. Murray said he had experience on the Secretary's Committee on *In Vitro* Fertilization which also held public hearings and that it is necessary to exercise tight control to avoid having certain people and certain viewpoints over-represented and dominating the floor. He urged the Chair to set up strong guidelines to avoid losing control of the situation.

Dr. McGarrity said he envisioned a similar process, as is used in the RAC, whereby he would open the floor first to RAC members to present their comments or suggestions, then to other people who have served on a subcommittee, followed by people who have requested time to speak, and then allowing people who walk in to make presentations. However, since it will not be known beforehand exactly how many people will be attending each meeting, there will have to be some flexibility in allowing speakers to make presentations in excess of the 5 minute time limit.

Dr. R. Murray suggested that the guidelines be spelled out in the interest of fairness, thus not allowing one person or group to over-represent their viewpoints. Dr. McGarrity noted that he has had some experience in these matters in the RAC and that he understood Dr. R. Murray's concern.

Dr. Clewell asked if the hearings would be recorded and transcribed. Dr. Wivel said he had engaged the same firm which currently prepares transcripts of the meetings of the RAC to send a representative. Complete transcripts would be made and a short distillation of each meeting prepared.

Dr. Miller said he remembered in Dr. Fredrickson's comments to the RAC that he speculated that perhaps it was time for the RAC's oversight of recombinant DNA to come to an end, except perhaps in the area of human gene therapy. He said he was concerned that this question was not one which was posed for discussion at the regional meetings.

Dr. McGarrity said he felt Dr. Fredrickson's comments were not aimed at asking the RAC to decide whether it needed to "go out of business," but that it should consider its future role. He said he felt the regional meetings were indeed a part of this process.

Dr. Miller said he felt the questions posed were an invitation to "tinker with the definition of 'recombinant DNA,'" and to include new processes. He felt the broader question of RAC oversight would have been a better issue to emphasize.

Dr. Atlas said he would like to see questions asked about process and whether the RAC should continue the dual role it has set up as being a "friend to the investigator" and helpful in developing protocols or whether it should be the "final arbitrator" and review the safety issues. He said he felt this question of process was an important one and that with many IBCs currently contemplating acting on requests for human gene therapy protocols, the regional hearings would be an excellent forum where this process dialogue can best be carried out.

IX. Future Meeting Dates of the Recombinant DNA Advisory Committee:

Dr. McGarrity called the committee's attention to tab 1397 which contains dates of future meetings. He noted the next meeting of the RAC is scheduled for October 16, 1990, which is the day following the regional hearing being held at the NIH.

X. Adjournment:

Having concluded the agenda and there being no further business to be discussed, Dr. McGarrity adjourned the committee at 12:21 p.m., on July 31, 1990.
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: 10/16/90

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