U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
MINUTES OF THE RECOMBINANT DNA ADVISORY COMMITTEE

May 30, 1991

TABLE OF CONTENTS

Dr. Anderson

X. **Proposed Addition to Appendix D of the *NIH Guidelines* Regarding a Human Gene Transfer Protocol Entitled *Autologous Transplantation for Chronic Myelogenous Leukemia: Retroviral Marking to Discriminate Between Relapses Arising from Residual System Disease Versus Residual Contamination of Autologous Marrow***
Dr. Deisseroth

XI. **Proposed Additions to Appendix D of the *NIH Guidelines* Regarding Human Gene Transfer Protocols Entitled *A Phase I/II Trial of High-Dose Carboplatin and Etoposide with Autologous Marrow Support for Treatment of Stage D Neuroblastoma in First Remission: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechanism of Relapse; and a Phase II Trial of High-Dose Carboplatin and Etoposide with Autologous Marrow Support for Treatment of Relapse/Refractory Neuroblastoma Without Apparent Bone Marrow Involvement: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechansim of Relapse***
Dr. Brenner

XII. **Proposed Amendment to Section I-C-2 and Deletion of Section III-A-2 of the *NIH Guidelines* Regarding Deliberate Release**
Dr. Hirano

XIII. **Background Information on the Registry of Gene Transfer Patients Entitled *The Gene Transfer Patient and Provider Network (Genetranet)***
Dr. Ledley

XIV. **Future Meeting Dates of the Recombinant DNA Advisory Committee and the Human Gene Therapy Subcommittee**
Dr. McGarrity

XV. **Adjournment**
Dr. McGarrity

The Recombinant DNA Advisory Committee (RAC) was convened for its forty-seventh meeting at 9:00 a.m. on May 30, 1991, 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, University of Louisville
John H. Barton, Stanford Law School
Al W. Bourquin, Ecova Italia
Michael F. Brewer, Dun and Bradstreet Corporation

Constance E. Brinckerhoff, Dartmouth Medical School
Nancy L. Buc, Weil, Gotshal and Manges
Ira H. Carmen, University of Illinois
Roy H. Doi, University of California, Davis
E. Peter Geiduschek, University of California, San Diego
Martin F. Gellert, National Institutes of Health
Robert Haselkorn, University of Chicago
Susan S. Hirano, University of Wisconsin
William N. Kelley, University of Pennsylvania Medical Center
Donald J. Krogstad, Washington University School of Medicine
Brigid G. Leventhal, Johns Hopkins Oncology Center
Brian F. Mannix, Buckland Mill Associates
Gerard J. McGarrity, Coriell Institute for Medical Research
R. Scott McIvor, University of Minnesota
Barbara E. Murray, University of Texas Health Science Center
Robert F. Murray, Jr., Howard University
Leonard E. Post, Upjohn Company
Moselio Schaechter, Tufts University School of Medicine
Executive secretary:

Nelson A. Wivel, National Institutes of Health

A committee roster is attached (Attachment).

Ad hoc consultant:

LeRoy Walters, Georgetown University

Non-voting agency representatives:

Daniel P. Jones, National Endowment for the Humanities
Henry I. Miller, Food and Drug Administration
Sue A. Tolin, U.S. Department of Agriculture

National Institutes of Health staff:

W. French Anderson, NHLBI
Jan Casadei, NCI
MaryEllen Franko, NCI
Christine Ireland, OD
Becky Lawson, OD
Debbie Wilson, OD

Others:

Paul Aebersold, Food and Drug Administration
M. James Barrett, Genetic Therapy, Inc.
Arindam Bose, Pfizer, Inc.
Malcolm Brenner, St. Jude Childrens Hospital
Yawen Chiang, Genetic Therapy, Inc.

Thomas Copmann, Pharmaceutical Manufacturers Association
Albert Deisseroth, MD Anderson Cancer Center
Sharon Durfy, Kennedy Institute
George Ferry, Baylor College of Medicine
Diane Fleming, Merck & Co.
Jeffrey Fox, Science Writer
Robert Goldberg, Merck & Co.
MaryAnn Grossman, University of Michigan
Winifred Hodge, University of Illinois
John Jaugstetter, Genentech, Inc.
Dorothy Jessop, U.S. Department of Agriculture
Daniel Kuebbing, Genetic Therapy, Inc.
Fred Ledley, Baylor College of Medicine
Robert Ledley, Georgetown University
Michael Lotze, University of Pittsburgh
Robert Moen, Genetic Therapy, Inc.
Robert Moody, Hoffmann LaRoche
Joe Palca, Science
Tomiko Shimada, Ambience Awareness International, Inc.
Paul Tolstoshev, Genetic Therapy, Inc.
George Walldrodt, Stenotech
John Whalen, Division of Standards Development & Technology Transfer
David Wheeler, The Chronicle of Higher Education
Lisa White, The Blue Sheet
Savio Woo, Baylor College of Medicine

I. CALL TO ORDER AND INTRODUCTORY REMARKS:

Dr. McGarrity, Chair, called the meeting of the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) to order at 9:00 a.m., May 30, 1991. He said the meeting was called pursuant to a *Federal Register* notice which, being 30 or more days prior to today's date, met requirements of the *NIH Guidelines for Research Involving Recombinant DNA Molecules*. He stated that the meeting would remain open to the public for its entirety, and that he expected the meeting to be of two days duration.

Dr. McGarrity noted a quorum was present and said every attempt would be made not to limit debate, but to keep the agenda moving, in hopes that all agenda items could be heard and discussed before members had to leave for travel purposes.

Dr. McGarrity stated that the RAC was advisory to the Director ofNIH and that any action taken by the committee was not binding on the NIH, but that Director may choose to accept, reject, modify or defer any recommendations or advice provided by the RAC.

Dr. McGarrity noted that he intended to make every effort to abide by the distributed agenda with respect to time estimates for each item of business. He reminded the committee that in recognizing persons for comments he would use the following order: primary and secondary reviewers on each item as set forth in the agenda; other members of RAC; *ad hoc* consultants to the RAC; NIH staff members; members of the public who had submitted written comments; and finally, other members of the public.

Dr. McGarrity welcomed the following new members who were attending their first RAC meeting:

Professor John Barton, Stanford University; Dr. Constance Brinckerhoff, Dartmouth Medical School; Professor Alexander Capron, University of Southern California; Professor Roy Doi, University of California at Davis; Dr. Robert Haselkorn, University of Chicago; and Dr. Brigid Leventhal, Johns Hopkins University. He noted that Dr. LeRoy Walters, Chairman of the Human Gene Therapy Subcommittee (HGTS) was also in attendance serving as an *ad hoc* member for this meeting of the RAC.

Dr. McGarrity then called on Dr. Post to introduce the next agenda item.

II. REVIEW OF THE MINUTES OF THE FEBRUARY 4, 1991 MEETING OF THE RAC:

Dr. Post said he had reviewed the minutes and found them to be consistent with his memory of what had transpired at the meeting. He suggested that Drs. Rosenberg and Blaese be given a chance to comment on sections which dealt with their presentations to ensure that the description of the technical portions of their comments were correctly reported in the minutes.

Mr. Mannix suggested several corrections of typographical errors and suggested that the Office of Recombinant DNA Activities (ORDA) staff could make these corrections in the final version of the minutes.

Mr. Mannix moved that the minutes be approved as amended by his comments. Dr. Gellert seconded the motion. There being no further discussion, the Chair put the motion to a vote. The motion passed unanimously with no abstentions.

Dr. McGarrity then called on Dr. Fleming to present the next agenda item.

III. PROPOSED AMENDMENT TO APPENDICES B-I-B-1 AND B-I-B-2 OF THE *NIH GUIDELINES* **REGARDING THE BACTERIAL ORDER** *ACTINOMYCETALES*:

Dr. Fleming noted that this proposed amendment was submitted in the name of the Mid-Atlantic Biological Safety Association and was compiled by herself, Dr. Joseph Van Houten of R.W. Johnson Pharmaceutical Research Institute and Linda Gulow of Hofmann-LaRoche.

Dr. Fleming said the proposal was to remove the gram-positive bacteria group *Actinomycetes* from the Group II fungi in Appendix B-I-B-2, and to include pathogenic bacteria of this order in Appendix B-I-B-1 of the *NIH Guidelines*.

Dr. Schaechter thanked Dr. Fleming for pointing out this taxonomic error in the *NIH Guidelines* which had grouped this gram-positive bacteria with fungi. He said he agreed with the concept of also only including pathogenic organisms of the order *Actinomycetales* in Appendix B-I-B-1. However, he pointed out that the list of six organisms supplied by Dr. Fleming seemed to be incomplete in that many of the submissions included with the proposal listed some 44 different known pathogens. He suggested that Dr. Fleming and her group review this listing and resubmit it for RAC consideration.

Drs. Krogstad and Brinckerhoff agreed with Dr. Schaechter's comments and both agreed that careful consideration needed to be given to which organisms were to be included in Appendix B-I-B-1 so as to avoid any further problems of a taxonomic nature in these appendices.

Dr. Fleming responded that she wished the RAC to make a formal motion on the removal of the *Actinomycetes* from Appendix B-I-B-2, and that she would be willing to take this list of proposed pathogens back to the Centers for Disease Control (CDC) and ask their opinion on a list of frank pathogens to be included in Appendix B-I-B-1.

Dr. Krogstad said he felt there was no way to make a formal motion on only the removal of the *Actinomycetes* from Appendix B-I-B-2, without leaving a void in the *NIH Guidelines* by not including them in some other appendix. He noted that this error had been in place now for 20 years and suggested that waiting another six months would not pose any problem. He asked Dr. Fleming to follow through with the CDC and return to the next meeting of the RAC.

There being no further discussion, Dr. McGarrity called on Dr. Lotze to present the next agenda item.

IV. PROPOSED ADDITION TO APPENDIX D OF THE *NIH GUIDELINES* **REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED** *THE ADMINISTRATION OF INTERLEUKIN-2, INTERLEUKIN-4, AND TUMOR INFILTRATING LYMPHOCYTES TO PATIENTS WITH MELANOMA***:**

Dr. Lotze said that because this protocol had been before both the HGTS and the RAC on previous occasions he would only discuss issues which had arisen at the previous RAC meeting and then would ask the primary reviewers to comment on the protocol.

He said that the Anderson-Blaese-Rosenberg protocol had shown that it was possible to introduce the neomycin-resistance gene into patients via the tumor infiltrating lymphocyte (TIL) and that both transduced and non-transduced cells can be grown which appear to have the desired biologic characteristic of G418 sensitivity. Furthermore, these cells can be detected in peripheral blood out to at least 2-3 weeks and in the tumor out as far as a couple of months.
Dr. Lotze said that the only major difference between the Anderson-Blaese-Rosenberg protocol and the one he was proposing was the incorporation of interleukin-4, another T cell growth factor, and that in every other respect this protocol is identical to that which was approved by the RAC for the National Cancer Institute (NCI).

Dr. Lotze said that his laboratory had demonstrated their ability to grow cells from human tumors in combinations of IL-2 and IL-4 and that cells so cultured can indeed be marked with the neo gene using the retroviral vectors. In addition, he noted that additional studies had been undertaken to expand over 15 different TIL preparations with combinations of IL-2 and IL-4 and cells had been transduced and/or selected. In all cases negative controls were used to look for neo expression and no such expression was found, however in situations in which the cells were selected for neo expression and grown in IL-2/IL-4 there was increased expression of neo.

Dr. Lotze underlined the fact that the company which will perform the PCR assays for them is capable of detecting down to 1 in 10 cells and that the plan is to have PCR done on clinical specimens by that company.

Dr. Lotze noted that one question that had arisen dealt with quantitation of lymphocytes in individual tissues. He said that after consideration of many techniques for accomplishing this, it was felt that standard immunohistochemistry would afford the most straightforward method of assessing this parameter. He presented a series of slides showing the ability of standard immunohistochemistry to quantitate lymphocytes in various tissue samples.

In conclusion, Dr. Lotze reminded the committee that this protocol had been through extensive review and modification and that due to this process many typographical errors had been made due to the multitude of changes that have been requested in the protocol. He noted that the investigators were anxious to begin the studies and hopeful of receiving RAC approval to proceed. He underlined that official approval is still needed from the Cancer Therapy Evaluation Program of the NCI as well as the FDA before the study can begin.

Dr. Gellert noted that this was the fourth time he had reviewed this protocol (2 times before the HGTS and once before the RAC) and that the protocol had changed in many regards. He noted that at the last meeting of the HGTS the major concerns were with how the gene-labeled cells could be quantitated and how a denominator for that measurement could be obtained by assaying the total number of lymphocytes in tumor, skin and muscle. He agreed that the standard immunohistochemistry method could be used to at least "semi-quantitate" the cells to derive the denominator. However, he noted that PCR measurements of the gene-labeled cells at the claimed sensitivity of 1 in 10 cells had still not been provided. He said that if there were contamination problems in the laboratory then samples sent to the company for analysis would not be usable at that level of sensitivity and therefore the interface between the laboratory and the company performing the PCR analysis needed to be proven. He noted that this could be accomplished by simply taking some comparable gene-marked cells, putting them into an animal system, re-isolating them and showing that the PCR assay would pick up down to the sensitivity level of 1 in 10 cells.

Dr. Gellert said that in light of this lack of hard evidence he still had doubts about approving this protocol to move forward.

Dr. Carmen said he felt the protocol now merited approval and that the informed consent document seemed to be "serviceable." He noted that the protocol in its present form is more readable and its intentions more focused than in previous versions. He said that the references that had been contained in the protocol which were irrelevant to RAC concerns had been removed and the gene transfer aspects of the study were enhanced. He added that he was persuaded that the risk of insertional mutagenesis did not warrant further scrutiny and that the informed consent document had been revised to address all of his previous concerns and that it was now much superior to its predecessor and more than sufficed for the protocol.

Dr. Post said that this protocol was really only a small step beyond what had already been approved in previous marked TIL experiments, that being the administration of IL-4. He said it had been clarified and that in general the data package was hard to follow in that certain figures and tables appeared without legends and explanations. However, he felt that Dr. Lotze had addressed this in his presentation. He said he would still like to hear more details of the PCR analysis to determine whether the sensitivity issue was resolved.

Dr. Post said one question involving the informed consent was the issue of skin and muscle biopsies. He said it was unclear as to what procedure would be used for obtaining these biopsies.

Dr. McGarrity called on Dr. Lotze to respond to the comments of the primary reviewers. Dr Lotze said that as far as the description of the skin and muscle biopsies in the informed consent, that at his institution it was general procedure to incorporate into a consent document details as to the risks associated with any procedure as well as descriptive terms of what is entailed in the procedure. He said he would be happy to revise the informed consent document and to incorporate additional comments so that the patient will be able to understand what skin and muscle biopsies entail.

Dr. Lotze then turned to the issue of thePCR assay and its sensitivity. He presented a data slide showing a PCR analysis and noted that the sensitivity data was much the same sort of data which was provided in the previously approved TIL protocol over a year ago.

Dr. Gellert said there was no question that laboratories can detect 1 cell in 10 byPCR analysis, however the question still remained as to whether it could be done in Dr. Lotze's laboratory. Dr. Anderson responded by saying that the same company which is currently providing PCR analysis for his experiments will provide the same service for Dr. Lotze, and that as long as the biopsies are taken properly, utilizing rubber gloves and placed in new containers, everything else would be automatically taken care of.

Dr. Leventhal said that if this was such a trivial matter, she was concerned as to why data had not been presented previously to the subcommittee and the RAC. Dr. Lotze said that he thought the issue of sensitivity had been resolved previously. However, he said this was a simple matter and that it could be done quickly. Dr. Gellert said that he would like to see such data and that he felt it was clear from the discussion at the HGTS meeting in April that such information was to be provided and he was surprised to have not seen it in the new package.

Dr. McIvor said one of the major concerns in the review of the protocol over the last few months had been the inclusion of control tissues to verify that any positive signal fromPCR in a tumor biopsy sample is actually due to homing of marked TILs to the tumor and not simply blood flow through the tumor. He said the only way to answer this question is to take muscle and skin biopsies. He said he felt the current informed consent document notifies the patient that such biopsies would be taken, but he was not sure it was made clear to the patient that this was not associated with an assessmen of the antitumor efficacy of the treatment but rather the biological characteristics of response from the therapy.

Dr. Walters noted that in the subcommittee meeting there was discussion as to whether there would be a separate consent form for the gene marking portion of the study. He said that in fact the motion that was passed asked the investigators to consider devising a separate consent form so that it was clear that the TIL cell therapy was one therapeutic protocol and the gene marking protocol was something distinct from that.

Dr. Lotze noted that a revised consent form had been forwarded toORDA which had evidently not gotten into the review materials for today's meeting. However, he produced a copy of it and asked that ORDA distribute them to the committee members.

Mr. Mannix asked if it were possible to approve the protocol subject to the condition thatPCR sensitivity on the order of 1 in 10 be demonstrated before beginning to treat patients. DrWivel said that he felt this would be one issue which would have to be resolved before the protocol were forwarded to Dr. Healy for her signature.

Dr. Leventhal questioned Dr. Lotze as to his techniques for obtaining skin and muscle biopsies. Dr. Lotze said that he intended to do a punch biopsy for skin and that he planned to do a needle biopsy for muscle since it is less invasive. However, he agreed that details regarding risk and a description of the procedures should be included in the document. Dr. Leventhal underlined the necessity for rewriting this portion of the informed consent document so that the patient was aware that by agreeing to take part in the study that they will have needles stuck in them that would not otherwise be stuck in them. Dr. Lotze agreed to rewrite this paragraph of the informed consent document and circulate it within the next hour if necessary. Dr. Leventhal said this would be fine.

Dr. McGarrity asked if Dr. Lotze was clear as to what was being asked as far as the informed consent. Dr. Lotze said that all the issues were clear to him and that he would draft wording to encompass the points made in the discussion. Dr. R. Murray added that it should also be noted that the frequency of the biopsies increases the risk of infection as a complication and that this should also be highlighted in the document.

Mr. Mannix then made a motion to table the agenda item until the new consent document was available. Dr. McIvor seconded the motion. Dr. McGarrity then put the motion to a vote. The motion to table passed by a vote of 17 in favor, zero opposed and one abstention.

Dr. McGarrity then adjourned the committee for the morning coffee break and asked the members to reassemble at 10:35 a.m.

Dr. McGarrity reconvened the committee at 10:35 a.m., and called on Dr. McIvor to present the next agenda item.

V. PROPOSED AMENDMENT TO *THE POINTS TO CONSIDER IN THE DESIGN AND SUBMISSION OF PROTOCOLS FOR THE TRANSFER OF RECOMBINANT DNA INTO THE GENOME OF HUMAN SUBJECTS* **REGARDING PRECLINICAL STUDIES:**

Dr. McIvor said he had raised this issue at the last meeting of the RAC in response to the review of several protocols at the November meeting of the HGTS in which it appeared that there had been a dearth of preclinical animal and, in some cases, *in vitro* experiments provided in these protocols and that he felt the best way to address this was to propose additional wording in the *Points to Consider*. The RAC suggested this be taken up at the HGTS for design of the specific wording. He said this was done and that under Section Two, "Preclinical Studies Including Risk Assessment Studies," the following wording is to be substituted:

> "Preclinical Studies Including Risk Assessment Studies: Provide Results that demonstrate the safety, efficacy and feasibility of the proposed procedures using animal and/or cell culture model systems and explain why the models chosen are the most appropriate."

Dr. McIvor said he felt this wording would indicate to the investigator writing the document that it will be their responsibility to demonstrate that there is some reason to expect that the procedure is safe and efficacious and that they must provide such data. He moved that this change in wording be adopted. Ms. Buc seconded the motion.

Ms. Buc asked why the language called for "the most appropriate" model rather than simply that the model system chosen is appropriate to demonstrate safety, efficacy and feasibility. She said the requirement should merely be that the model suit the scientific purpose to which it is being put. Dr. McIvor said that the availability of models is limited and in most cases what is being sought is a demonstration of gene transfer into human material, and in most cases he felt this is what the investigators will provide in the end.

Dr. Anderson said he felt it was up to the investigator to determine what the most appropriate model was and that factors needed to be taken into account such as the expense and other problems of the

model system. He said he felt the term "most appropriate" does not place additional restrictions on the investigators than is currently in place.

Mr. Mannix said he was sympathetic to the proposed changes, but was concerned that some of the precedents being set may create inadvertent monopolies in that researchers may perceive that the only laboratory that's acceptable to the RAC for doing PCR amplification is the one currently being used by the researchers who have had protocols approved thus far and that it is not worthwhile to attempt something new because the RAC has already deemed this procedure as the most appropriate one.

Dr. McIvor said there were many techniques available to assess safety, efficacy and feasibility and PCR just happens to be one that is very sensitive. He noted there were different model systems that one could use to assess what might occur in humans which would provide preclinical data to assess the efficacy of the proposed procedure.

Mr. Mannix said he was concerned with requiring demonstration of efficacy in a Phase I study where safety was the only issue being addressed. Dr. McIvor responded that even in a Phase I study there must be some anticipation that the proposed protocol will eventually be efficacious and therefore preclinical data must be provided before such a procedure is launched.

Dr. B. Murray said she felt one problem was the interpretation of the term "most appropriate," in that it could be interpreted in different ways and may provide a problem in assessing proposals. Dr. Anderson said the concern of most investigators he had spoken with was that they were concerned that the situation may occur in which the investigator has done everything that they think is appropriate, however a very influential or strong-willed member of the RAC or the HGTS might say, "I don't think that's the best model, that it should be done in such-and-such a model," and that the reviewers will not accept the model which was deemed most appropriate by the investigator.

Mr. Barton suggested, as a friendly amendment to Dr. McIvor's motion, that the word "most" be dropped from the wording. Dr. McIvor said he would accept this as a friendly amendment and that he felt it still expressed the intent of the proposed wording. Dr. R. Murray suggested, in the form of a friendly amendment, that the last sentence be modified to read, "...the models chosen are appropriate for the protocol." He felt that this wording would force the investigator to prove that the model proposed was appropriate for that protocol and that, at the same time, it would not restrict the investigator to a single model.

A lengthy discussion ensued centering on the specific connotation of the term "efficacy" as to whether this implied "therapeutic efficacy." It was determined that the term "efficacy" in this sentence should be taken as the efficacy of insertion of the marker, rather than therapeutic efficacy for the patient.

Dr. McGarrity then restated the proposed wording, as amended, as follows:

> "Preclinical Studies Including Risk Assessment Studies: Provide results that demonstrate the safety, efficacy and feasibility of the proposed procedures using animal and/or cell culture model systems and explain why the models chosen are appropriate for the protocol."

There being no further discussion, Dr. McGarrity called for a vote on Dr. McIvor's motion. The motion passed a vote of 17 in favor, 1 opposed and no abstentions.

Dr. McGarrity then called on Dr. Ledley to present the next agenda item.

VI. PROPOSED ADDITION TO APPENDIX D OF THE *NIH GUIDELINES* **REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED** *HEPATOCELLULAR TRANSPLANTATION IN ACUTE HEPATIC FAILURE AND TARGETING GENETIC MARKERS TO HEPATIC CELLS* **:**

Dr. Ledley said the research being proposed, in the broader sense, was to treat a genetic disease of the liver by removing cells from a patient by partial hepatectomy, growing hepatocytes in culture, transducing them with a vector to repair the genetic defect in the cells, perhaps selecting for the cells in which the defect has been repaired and then transplanting those cells back into the patient.

Dr. Ledley said the proposal is to find children who have fulminant hepatic failure or life-threatening liver disease for whom transplant is not available in time to save their lives or to prevent severe mental retardation, and to try hepatocellular transplantation either to palliate their hepatic failure and provide a bridge to recovery or to perhaps even reconstitute the liver with donor cells. He noted that the LNL6 vector will be introduced as the genetic marker to assess the phenotypic effect on the patient and to assess engraftment of the transplanted cells.

He noted that because the clinical issues of this research are difficult to assess, there are a series of associated clinical research protocols which will accompany this gene transfer protocol and as well a psychosocial protocol to address the difficult issue of informed consent which will include an assessment of the informed consent documents by means of a quiz to determine if the parents gained knowledge and insight into the procedure via the informed consent documents. He also added that a study is underway in which laboratory personnel are being screened for the presence of amphotrophic retroviruses and that currently there is no evidence to support any adverse exposure to laboratory workers. However, blood from laboratory workers is being frozen to ensure this safety issue is addressed. And finally, the team is going to suggest a registry be developed so that adverse reactions can be identified and the best long-term care can be provided to these patients.

Dr. Ledley said the primary issue listed in the *Federal Register* was to show that human hepatocytes could be transduced with the retrovirus. He noted that there were no samples of human hepatocytes available until two weeks prior to this meeting and that he had just received the data via Federal Express while at the meeting. He noted that Dr. Woo, a co-investigator, would present additional data on the hepatocellular transplantation in the mouse using a new detection method utilizing a fluorescent stain called diI, as well as an experiment performed in a baboon within the last month showing the feasibility of the approach.

Dr. Ledley presented results of studies on residual liver from reduced orthotopic liver transplants which showed that one can prepare hepatocytes, culture them, and transduce them with a beta-galactosidase virus to show the right cells are being infected and then detection of LNL6 provirus using a PCR assay down to a sensitivity level of 1 in 10 or possibly even 1 in 10 cells

Dr. Ledley then called on Dr. Savio Woo to present follow-up information on a dog experiment which was previously reported to the HGTS. Dr. Woo said that the dog was chosen as an intermediate model because going from the original mouse model to a human was too big a jump. He said 10 animals were done during the past 6 months in an attempt to learn how to isolate hepatocytes after

partial hepatectomy. Initially only 10 cells were isolated from a single lobe from a dog, but that now they can consistently isolate 3 billion hepatocytes from a single lobe, which is 20-25% of the liver mass of the animal.

Dr. Woo said that initially they attempted to transplant non-transduced hepatocytes by direct injection into the spleen but that complications arose which forced them to seek another route of transplanta tion. They investigated the feasibility of transplanting the cells directly into the mesenteric vein, the splenic vein and the splenic artery by use of a catheter. Via this technique they were able to transplant 1 billion cells into each of the routes and are now satisfied that they have the technology for transplanting hepatocytes into these larger animals. They then used hepatocytes isolated from a dog and transduced with human a-1-antitrypsin containing retrovirus and performed autologous transplantation. This produced large bursts of the human marker protein in the blood during the first couple of weeks, which receded and dropped to zero after a month. The animals were then sacrificed and different sections of the livers were looked at via PCR analysis for the presence of the provirus. Four of 8 spots from the liver showed positive by ethidium staining and additional blots are being examined to date. He said that he wanted to know what percentage of the transplanted cells were actually recoverable from the liver and that until quantitative data is in hand he would be reluctant to make any estimates. However, the research is still ongoing and results are expected within a week.

Dr. Ledley then turned to the question ofquantitation of the transplant and its relationship to how many cells they can get into an animal. He said that he felt the most appropriate animal model for this was the baboon. He presented data on a 2 year old baboon that was being sacrificed because of a seizure disorder in which the investigators were able to perform a left laterallobectomy. They were able to harvest hepatocytes and stain them with the fluorescent dye diI, which is an extremely hydrophobic molecule which binds to membranes and is extremely fluorescent as well as being absolutely stable *in vivo*. It does not transfer from cell to cell and it can be used to track single neurons and their projections. The cells were stained and transplanted into the spleen of the animal using 2 X 10 cells per kilogram, which is the same level proposed for the human experiments. Then the animal was sacrificed a week after the transplant and histology showed the animal to be normal. Donor cells could not be discriminated from recipient cells on H&E section.

Dr. Ledley noted that one question which had been brought up was whether these cells could be found throughout the liver or whether you had to biopsy in the right place to find them. He said that they looked at 13 segments of liver from all different regions and no differences could be found. What was seen in 2 out of the 13 sections were small emboli in some of the small portalvenules, but no evidence of infarction or damage to the liver resulting from these cells. In the spleen the cells could be found within the splenic pulp, therefore showing that clearly in the baboon this did engraft well. On counting, 5 percent of the total cells counted were found to be fluorescent, thus reflecting the exact prediction of what would be found in the animal by putting in 2 X 10 cells per kilogram.

Dr. Ledley said the question then was can the cell which takes up the provirus which is then implanted be detected. He said this depended on the following three variables:

1. Transduction efficiency;
2. What fraction of donor cells originate from the transplant; and,
3. How sensitive are the methods of detection.

Dr. Ledley said that he believed this experiment shows that they can detect cells to a sensitivity level down to 1 in 10, which is consistent with the preclinical data presented.

As far as the appropriateness of animal models, Dr. Ledley said that this varied depending upon the aspects which were being looked at. For surgical aspects of the experiment the dog is thought to be the most appropriate model. Mice are the most appropriate model to look at transplant efficiency because of the ability to engineer all sorts of genetic markers in them. And despite the desire to do more primate models, they are a scarce resource and not generally available for use in this research.

Dr. Ledley then went on to discuss why an exogenous marker is needed when a heterologous transplant is being proposed. He said all other forms of assays do not possess the specificity and sensitivity exhibited by the provirus PCR assay and therefore it has extreme advantage over *in situ* hybridization, HLA antigen testing and DNA polymorphism assays. He noted that the provirus PCR assay is extraordinarily sensitive and possesses the advantage of being able to have the same marker in every patient, thus allowing for good quantitative comparisons between patients.

Dr. Ledley then introduced Dr. George Ferry to discuss the patient selection procedures, which is central to the ethics issues surrounding the proposal.

Dr. Ferry noted that the major problem faced with children is that the majority of acute liver disease and liver failure is in very young children where the availability of organ donors is the poorest. He said this protocol had been set up to use children with acute fulminant liver failure who were not expected to live longer than a few days or a week or two at most who would be eligible for liver transplantation if such a donor organ became available. In this age range survival in infants and young children is less than 10% as a rule and that it is difficult to ascertain which patient, if transplanted, would survive and which would die. Further, he noted that young infants with metabolic defects and fulminant necrosis and liver failure are at incredible risk for early and severe brain damage with subsequent death early on or a lifetime of total handicaps and inability to function as an adult. These patients are also transplantable, however even by a month of age some have already suffered so much brain damage they're no longer eligible for transplantation.

Dr. Ferry said that all the clinicians dealing with liver disease are encouraged with the prospects of transplantation, despite the drawbacks of high cost for transplant procedures as well as the 80-90 percent survival rate in moderately ill patients. However, he felt that there was a need to develop a process whereby a patient will not be faced with a lifetime of cyclosporine use with its inherent toxicity and that this was a major drawback to liver transplant.

Dr. Ferry concluded his remarks by noting that despite the fact that the effectiveness of these cells decreases over time, he felt that did not detract from the significance of doing hepatocellular transplantation in that even in patients with fulminant failure and necrosis it could buy as much as a month's time with functioning hepatocytes, therefore allowing more time to obtain a transplant donor organ.

Dr. McGarrity then called on Dr. McIvor to begin the review. Dr. McIvor noted that he had also been a primary reviewer for the HGTS meeting in April. He said he would only cover the major points pertinent to the review of the protocol which were brought up at the HGTS and explain how those had been addressed in the materials and today's presentation.

Dr. McIvor said the first issue was safety. He noted that the same retrovirus (LNL6) was proposed to be used in this protocol had already received FDA approval. However, he noted the major safety consideration related to the fact that hepatocytes were to be transduced rather than lymphocytes or bone marrow cells and that the risk of insertional mutagenesis was the major safety concern. He noted that the investigators had done an adequate job of estimating the probability of insertional mutagenesis in their supplemental materials and, despite there being a certain amount of unpredictable risk associated with this, it was not a major concern and that the investigators were aware of it.

Dr. McIvor said his second concern dealt with the actual migration of donor cells to the liver since this was a major issue in being able to detect tagged cells present in the liver and therefore a key factor in the feasibility of the proposed protocol. He noted that in a recent *PNAS* article by Ponder, *et al.*, the indication was that this number of cells would be 1 in 1,000. However, the baboon data provided in the supplemental material shows that it is possible to have as much as 5% of cells from the donor in the recipient organ.

Dr. McIvor said one of his concerns in the review for the HGTS meeting was the lack of information on transduction frequency and he said he felt the material presented this morning relative to this issue reassured him that PCR could be used to determine the presence of sequences with a sensitivity of 1 in 10. He noted that one major question still remained in terms of transduction frequency and that was that the current experiments that were done with human hepatocytes needed to be scaled up to a level of 10 hepatocytes to test the feasibility in humans. He invited Dr. Ledley to comment on this.

Dr. McIvor said he had questions also in terms of the evaluation of engraftment. His main concern was the application of PCR. He said he did not believe this was a major block to approving the protocol since Dr. Ledley had, in fact, provided some maps specifying exactly how the PCR would be done which demonstrated the sensitivity was at a level of 1 in 10, which is a level necessary to detect the presence of the marker in the recipient liver. He said one other question he had was if one could perform *in situ* hybridization on liver samples to detect expression of the neo gene that this could possibly be a superior method of determining whether or not the marker was there. He asked Dr. Ledley to update the committee in terms of the development of *in situ* hybridization and confocal microscopy.

Dr. McIvor noted that he had asked Dr. Ledley to look into alternative methods of evaluation of engraftment since one of the major limitations in detecting donor cells by genetic tagging is that only a portion of the cells are actually tagged; these cells should be distinguishable on the basis of natural biologic polymorphisms. One method which Dr. McIvor suggested needed to be looked at was the Y-specific protein or surface markers associated with the MHC, but he noted that these techniques had not yet been established for liver samples and therefore using these them would require major technical work-up before they could be assessed. Dr. McIvor said that Southern analysis is used for detecting genetic polymorphisms in bone marrow engraftment and he did not know whether PCR had been used in this respect. He asked Dr. Ledley to comment on this.

In summary, Dr. McIvor said the major reservation of the subcommittee was that there needed to be a feasibility assessment and that he felt this had been accomplished now by these investigators.

Dr. Bourquin said he thought the investigators should be complimented on the thoroughness with which they addressed all the issues brought before them. He said that essentially he felt the comment could be lumped into two questions:

1. Will it work? and,
2. Is it necessary?

He noted that both of these questions were discussed during the presentation by Dr.Ledley and his coworkers. The first question was addressed in terms of the genetic marker and the sensitivity with which valid results are expected. The second question was also addressed by a sentence from the materials provided by Dr. Ledley:

> "The use of the genetic marker appears to add minimal, if any, risk to the patient while greatly enhancing the probability of obtaining a meaningful result and gaining knowledge of value from the experiments."

Dr. Bourquin said other issues included in the subcommittee's review included the ability to pay and how patients were selected. He noted the investigators had stated that only patient who were financially eligible for organ transplants could enroll in this program. However, they had now amended this slightly and provided the following statement:

> "But to avoid the opposite problem of denying treatment to those financially unable, the investigators are working very hard to obtain additional funding through Medicaid to support these patients as well."

Dr. Bourquin said he felt that now, in light of this, that the program was open to anyone who meets other standard clinical criteria. He noted the investigators had changed the consent form and provided evidence that their informed consent program has demonstrated a significant increase in knowledge of the procedures following a review of the materials provided to the patients and that it was apparent that this program was providing a good information transfer.

Mr. Barton said that a central point to be considered in this protocol was that it was an experiment in children and that he felt the committee needed to be very careful about the degree of risk which people were being asked to undertake for altruistic purposes. He also said that he felt that if this protocol were approved that the committee would, in essence, be saying that the LNL6 system is the marking system of choice where there is anything but a very obvious alternative. He said he was comfortable in doing this in this case, in light of the risks and problems of the children, but nevertheless he felt it would be very difficult in the future to say no to the use of this vector in any situation.

In regards to the informed consent, Mr. Barton said the assent form needed to describe the marking procedure and a statement outlining the altruistic nature of the assent should be included. On the main consent form he said he felt the vector was being compared to routine vaccines for mumps and measles and that he was uncomfortable with this because it suggested a degree of familiarity or routineness of the procedure which was unfounded. He urged that the investigators remove that sentence from the consent form.

Dr. McGarrity then asked if other members of the RAC had questions that needed to be responded to by the investigators.

Dr. Krogstad asked the investigators to address the issue of whetherhepatocyte cell lines were currently available to the investigators.

Dr. Post noted that the proposed dosage was 2 X 10 cells per kilogram and asked whether this constituted the maximum tolerated dose since this was the highest dosage noted in the preclinical data. He asked Dr. Ledley to comment on dose selection.

Dr. Atlas said that he noted that in the preclinical data there appeared to be a time when the surgical procedures were changed and resulted in an increased survival of the animals. He asked what change in procedure caused this increased survival.

Dr. Walters said that he had noticed that the consent form lumped hepatocellular transplantation, bone marrow grafts and gene marking together and asked whether patients would be allowed to receive one without the other.

And Dr. R. Murray noted that the consent form (page 1455, paragraph 6) referred to risks associated with blood and blood products in a transplanted patient. He noted that it stated:

> "These risks will be the same as those associated with whole organ transplantation and will be explained to you by the transplant team."

He said he did not see any other mention of these risks in the consent form and asked why they were set apart and what assurances existed that these issues will be addressed by the transplant team.

Dr. Ledley noted that the issue of scale was very important. He said the most critical step was in the hepatocyte preparation. He said they had gone ahead and prepared a whole organ just to prove it could be done and used the same type of conditions that were planned to be used in the protocol for the infection, although they limited numbers of plates for cost purposes. He noted that they were not proposing any modern or sophisticated methods of dealing with this large number of cells, but noted that this procedure would be the same one used during the experiment.

On the issue of alternative methods, he noted that there were two clinical models which he had discussed at the HGTS to look at the question of detecting a small population of cells among a larger population of unrelated cells. One is the use of PCR analysis, although the limit of sensitivity is never pushed to the limit needed for use in such a protocol. The other is fetal sexing, or Y chromosome analysis, which he said is the more appropriate model to be used in such experiments, and then to perform PCR or *in situ* hybridization techniques to look for mutations and do linkage analysis. He noted that this technique is very difficult and as yet is unproven.

Dr. Ledley noted that the team intends to look at a very small number of subjects (6) to see if the marker gene is necessary to detect successful engraftment. He said that if it proved successful the plan was to turn the surgeons loose to perform the engraftments without markers. However, if better markers are needed or discovered, they would switch to those better markers. He noted that

retroviruses at this point appear to be the only markers available to do the experiment. He noted that he had tried the *in situ* hybridization assay and the results are not yet available to confirm it, but that he felt that this coupled with confocal microscopy could be the best method for detecting successful engraftment.

He said that as far as the diI was concerned there was some question as to its toxicity in humans and would require FDA approval.

He noted that as far as the consent form went, the questionnaire had been tested on their nursing staff and that it will continue to be studied in the patient population to study its validity in this population.

Dr. Ledley said that there were no hepatocyte cell lines available and that they had done extensive work in human hepatoma cell lines and those models would be used for many of the proposed studies, especially work on transduction efficiency required for gene therapy.

He said the dosage had been worked up through the preclinical experiments and that there is an elaborate calculation in the original proposal of how many cells this will amount to relative to total liver mass and many variables. He noted that future animal experiments will continue to push this dose up, but that what is being contemplated here is a dose which has been administered without complication in preclinical experiments.

He noted that they had also experimented with different infusion media and that after experimentation with various media this has ceased to be an issue.

Dr. Ledley noted that patients were made aware of many of the risks of liver transplant via a publication outlining the procedure as well as undergoing counseling with a nurse coordinator who is able to answer any questions they may have. He underlined that all patients are therefore fully informed of the procedures involved as well as the risks of liver transplantation.

In response to Dr. Walters' question as to whether the investigators would carry this experiment out without the marker gene, Dr. Ledley replied that the preclinical data on this point is mixed but noted that the surgeons felt they could use classical surgical methods to accomplish the transplant. However, he noted he felt the marker gene was important for verifying and confirming the success of the transplant.

Dr. McIvor asked what was the maximum number of human hepatocytes which had been transduced and what kind of transduction frequency had been seen. He also asked if Dr. Ledley intended to transduce 10 cells. Dr. Ledley said that would be the case for a 50 kilogram person, but noted that the patients they would be working with were children who would be in the weight range of 5-20 kilogram. Therefore, for a 10 kilogram patient they would transduce 2 X 10 cells which would be comparable to the levels which were used in both the baboon and dog models. Dr. Woo added that in animal experiments using a human alpha-1-antitrypsin stain they were able to transduce 2-3 billion hepatocytes in culture and that they found that approximately 20 percent stained positive for the human gene.

Dr. McGarrity noted that there were no human hepatocellular cell lines, and he asked if attempts had been made to develop an immortalized cell line. Dr. Ledley said hepatocytes will sit in tissue culture and express hepatocyte markers for months, but that they stop dividing after the first 4-5 days. However, he noted this is an active area of research and that attempts were being made to alter the

media to get these cells to continue growing.

Dr. Kelley said he felt that for completeness sake he felt it important that DrLedley should check out the use of dii to make sure it's not FDA-approved because this could be an alternative approach which could prove valuable if it were not carcinogenic or toxic in humans. Dr. Ledley noted that dii had only been in use for a short period but he said he would attempt to clarify this.

Dr. Atlas asked for further clarification on the changes in procedures which resulted in improved survival of the animals after surgery. Dr.Ledley reiterated that this was a combination of changing the media over to Ringer's solution and phosphate-buffered saline as well as improvements in surgical technique.

Dr. McIvor asked if the investigators had ever contemplated using another virus vector, such as a beta-galactosidase vector, which would give improved detection. Dr. Ledley said they had been doing work on an alpha-1 virus which offers some excellent prospects for the future. He said the issue is that the LNL6 has already received FDA approval and the investigators did not feel it was necessary to go to the time and expense of attempting to get another vector approved in light of the nature of the experiment, which is merely to test the feasibility of the process. However, he noted that work would continue on these other vectors and that if this feasibility experiment proves successful that the next step would be to look at this issue. Further, he noted that such research on a new vector would best be performed with adult subjects, rather than children.

Dr. R. Murray asked what tests were intended on being performed on the donor livers prior to transplantation. Dr. Ledley said they would be tested the same as any tissue prior to transplantation including tests for cytomegalovirus, hepatitis B virus and HIV. Dr. Murray asked that this information be included somewhere in the informed consent. Dr. Ledley agreed and said he would amend the informed consent form to include such information.

Dr. Kelley asked what proportion of total hepatocytes was being contemplated for infusion into the patients. Dr. Ledley said that based on mathematical calculations assuming the patient to be a prototypical 70 kilogram person and if 10 cells were infused, this would constitute approximately 5 percent of the total hepatocytes in the recipient. He said this figure matches both the baboon and dog experiments. However, he noted that in some of these patients withfulminant viral hepatitis, et cetera, they may have lost a significant proportion of theirhepatocytes prior to induction and therefore the percentage could be much higher, but he added that in such cases the cells would be subject to the same growth factors, et cetera, present in the patient. He said further experimentation is required, but that of course the optimum would be for these induced cells to proliferate and repopulate the entire liver, but that he didn't suspect this would be the case.

Dr. McIvor then said that he was satisfied that the investigators had addressed all the issues and moved that the protocol be approved contingent upon the suggested changes in the consent document which were raised in the meeting. Dr. Bourquin seconded the motion. Dr. McGarrity then asked for further discussion on the motion.

Dr. Kelley reiterated his concern that the investigators look atdiI and determine whether or not it was an acceptable alternative hepatocellular marker.

Dr. McIvor suggested that the committee put together a list of all changes which need to be made to the consent form, so that both the investigators, as well as the RAC, are clear on exactly what will be done. The following listing was compiled by the committee:

1. Deletion of the reference to measles and mumps;

2. Insert the statement, "This will not necessarily help me, but may help others" in the assent form;

3. Inclusion of information on the risk ofCMV, HIV, hepatitis and other risk factors associated with the donor material in the informed consent form;

4. On page 1455, paragraph 7, line 2, replace the term "genetic marker" with "bacterial marker."

There being no further discussion, Dr. McGarrity put Dr. McIvor's motion to a vote. The motion passed by a vote of 18 in favor, none opposed, and no abstentions.

Dr. McGarrity noted that the approval of this protocol was important in that it broadens the target cells beyond lymphoblastoid cells and expands the diseases being investigated beyond cancer and birth defects. He noted that this also provided the field with another center now working on human gene therapy which has been dominated by NIH to this point. He thanked the investigators and reviewers for their efforts.

Dr. McGarrity said that the LNL6 vector has become almost analogous to the*E. coli* in the early days of recombinant DNA research. He noted that on the one hand that is good in the sense that it is building an historic data base. However, on the other hand, it could discourage innovation and development of alternative vectors. He said it was important to encourage alternate proposals that may answer some of the questions that LNL6 will be unable to address.

Dr. McGarrity then adjourned the committee for lunch and asked them to reconvene at 2:00 p.m.

Dr. McGarrity called the RAC to order at 2:05 p.m. He noted that several members were attending their final meeting as members of the RAC. He thanked them for their service and presented them with certificates from the NIH commemorating their service to the RAC. These members included: Dr. Atlas, Mr. Brewer, Dr.Gellert, Mr. Mannix, Dr. McIvor and Dr. R. Murray.

Dr. McGarrity then called on Dr. Carmen to continue discussion of Item IV, which had been tabled from the morning session pending some changes to be made in the protocol.

VII. PROPOSED ADDITION TO APPENDIX D OF THE *NIH GUIDELINES* **REGARDING A HUMAN GENE TRANSFER PROTOCOL ENTITLED** *THE ADMINISTRATION OF INTERLEUKIN-2, INTERLEUKIN-4, AND TUMOR INFILTRATING LYMPHOCYTES TO PATIENTS WITH MELANOMA***:**

(Continuation of discussion)

Dr. McGarrity noted that there were two issues still remaining to be discussed on this protocol: (1) the informed consent document; and (2) conditional approval pending the receipt of quantitative

data on the PCR studies.

Dr. Carmen said he would defer comment to those who had questions on these issues. Dr. Post said he would vote to approve the protocol. Dr. R. Murray said he felt that the issue of infection related to taking biopsies needed to be clarified and that although the risk was minimal, it should be stated clearly in the informed consent document.

Dr. Walters asked whether it were possible for a patient to undergo the interleukin andTIL therapy but not take part in the gene marking study. Dr.Lotze said there was no requirement that all patients undergo all parts of the study in order to receive the therapy. He agreed to add a sentence to the informed consent form to make this clear.

Dr. Gellert moved that the RAC grant conditional approval to this protocol pending receipt of data on the quantitative aspects of thePCR. Dr. Post seconded the motion. Dr.McGarrity called for further discussion on the protocol.

Dr. Hirano noted that the protocol had been divided into four arms with 5 patients in each arm. She asked how many of these patients would actually receive the treatment. Dr.Lotze clarified that the plan is to have all patients treated. He said that the earlier version of the protocol specified four groups, but that this had been amended and the different approaches concatenated into a single protocol.

There being no further discussion on the proposal, Dr. McGarrity called for a vote on Dr. Gellert's motion to conditionally approve the protocol pending receipt of the results of thePCR analysis. The motion passed unanimously by a vote of 18 in favor, none opposed and no abstentions.

Dr. McGarrity then noted that Dr. Gellert had been out of the room when he presented certificates of service to other retiring members of the committee and he presented DrGellert with his certificate and thanked him for his service.

Noting that the meeting was running ahead of the contemplated schedule, Dr.McGarrity called on Dr. Anderson to present an update on the ADA gene therapy studies that had been approved by the RAC previously and which were now ongoing at NIH.

VIII. UPDATE ON THE ONGOING ADA HUMAN GENE THERAPY TRIAL:

Dr. Anderson said the first patient had started therapy on September 14, 1990 and had now had 6 infusions. A second patient had been started on January 31, 1991, and this patient has had 3 infusions to date.

He said the first patient has continued to improve in every aspect of her existence and that approximately three weeks previous she had been challenged with a tetanus toxoid vaccination which took and was a very strong positive and she continues to do well in terms of not being ill. He said the investigators were concerned that the parents had begun to treat the child as if she were normal and that there still should be concerned since she still is at risk of lethal infections due to an incomplete immune system.

Dr. McGarrity asked about her levels of isohemagglutinin. Dr. Anderson said that these are now normal. Dr. McIvor asked what level of ADA was present in the blood stream of the patients and what fraction of cells are ADA-positive or positive for transduction with the virus. Dr. Anderson said

that as far as ADA in the blood stream was concerned, the patient was now up to roughly 20 percent of normal. He said that PCR analysis showed approximately the same insofar as fraction of ADA-positive cells, that is 20 percent, but that this leads to a concern that as she continues to increase the percentage of gene-corrected cells had has a higher and higher percentage of these cells that by taking cells out every month and adding the additional ADA gene to them that they will indeed begin to add second and third genes to cells which already possess the ADA gene. He said the investigators were looking into ways of trying to pan out cells that are already corrected from the pool being taken out so that they only are correcting cells which do not possess the ADA gene. He noted further that once 50 percent of cells contain the ADA gene the investigators intend to stop and wait and see how long she can then go on her own without further infusions.

Dr. Miller asked if there was any evidence of antibodies to ADA or neutralizing antibodies in the patient. Dr. Anderson responded by noting that there is no such evidence yet, although the patient is making CRM (cross-reactive material) and therefore there is some evidence that she is making something.

Dr. McGarrity asked if the investigators could distinguish between the PEG-ADA and the recombinant ADA in the patient. Dr. Anderson said this was easily distinguished since the PEG-ADA is a bovine preparation and it was only found in the circulation.

Dr. Miller asked if the investigators contemplated withdrawal of PEG-ADA as they had originally considered. Dr. Anderson said the intention was to give the patient at most 3 more infusions and then to stop and follow her for a period of time and do a complete immune analysis. If the gene-corrected cells continue to have a selected growth advantage then the investigators will submit Part III of the protocol to the RAC for review since it would be at least a year before they would consider removing the PEG-ADA from the patient. However he voiced concern that they may not be able to remove the PEG-ADA due to safety concerns as to whether she can maintain herself in a fully detoxified state with only 50-60 percent of T cells making ADA. He said that if, after removal of PEG-ADA, there were any danger at all she would be put back on the PEG-ADA.

Dr. Walters asked how Dr. Anderson would respond to the possibility that the therapeutic benefit being seen in the patient thus far was primarily due to the large number of T cells that were being infused in her, rather than the genetic modification. Dr. Anderson said that there was a flaw in the protocol in that there is no control to assess this. He noted that in order to control for this it would be necessary to do exactly the same protocol but to put in the LNL6 gene instead of ADA and see whether she was helped just as much by simply having her T cells grown up and returned to her. However, he said he did not believe this to be ethical in that the investigators have always felt that in theory the best bet to achieve success would be to correct the defective T cells so that they became normal T cells. He noted that time would give the appropriate answer but that the investigators felt from a clinical point of view this was a control which they did not wish to undertake from this ethical viewpoint.

Dr. McGarrity thanked Dr. Anderson for his report and asked him to present the next item on the agenda.

IX. PROPOSED AMENDMENT TO THE *POINTS TO CONSIDER IN THE DESIGN AND SUBMISSION OF PROTOCOLS FOR THE TRANSFER OF RECOMBINANT DNA INTO THE GENOME OF HUMAN SUBJECTS* **REGARDING THE HUMAN GENE THERAPY SUBCOMMITTEE BE ELIMINATED FROM THE REVIEW PROCESS INVOLVING HUMAN GENE THERAPY PROTOCOLS:**

Dr. Anderson said he would address what he considered to be the advantages and disadvantages of the proposed amendment. He said there were three misconceptions that had come to light in the various written comments received which he felt needed to be addressed concerning this proposal:

1. That there should be less review of human gene therapy protocols;

2. That investigators were unhappy with the Human Gene Therapy Subcommittee for various reasons; and,

3. That there was a feeling that the RAC was not capable of doing as good a job of reviewing human gene therapy protocols.

Dr. Anderson said that one advantage of the proposal would be to make the RAC the primary body with the ability to make the most informed decision on a human gene therapy protocol. He said at present the subcommittee goes through the technical details and when the protocol comes before the RAC it merely sees a summary of what has happened and is asked to ensure that any questions posed by the subcommittee are answered. He said he did not believe that the RAC is making the kind of informed decision that it could and should be making on these protocols.

Dr. Anderson said he doubted the RAC would vote today to dissolve the HGTS, but that his aim in submitting this proposed amendment was to start the RAC thinking about when and how to phase out the HGTS and how this expertise could be conserved by making the members of the HGTS simply *ad hoc* members of the RAC. He said he felt that as RAC members are replaced that possibly what should take place is that these replacements come from the HGTS.

Dr. Anderson said he felt there was a duplication of effort in the current process which results in the RAC not being as informed as it could be. He suggested that the RAC could meet four times a year instead of the three times it currently meets, and by doing so ORDA's job of having to put together duplicate materials for meetings as well as the time of many reviewers who serve on both committees would be conserved. He noted that Dr. McIvor had objected to this concept on the basis that some protocols would take longer to receive approvals. Dr. Anderson said that he felt the good proposals would in fact get quicker approval, while poorer proposals may move slower, but that overall this would be an advantage to the field by having the good proposals being more quickly approved.

As far as the disadvantages to abolishing the HGTS, he said it could be viewed by some that this was resulting in less review and many critics of human gene therapy could be expected to say it is too early to abbreviate the review process. However, Dr. Anderson said he did not think the general public knew or cared who actually performed the review, so long as there was not a perception that it was a less careful review. He said that on the other hand this would send a signal to investigators, pharmaceutical companies and research institutes who may be interested in moving into this area, that the process is straightforward and appropriate and is being made more efficient by abolishing the HGTS.

Others criticize that to dissolve the HGTS would be to make the review process less intense. Dr. Anderson underlined that at present any protocol must undergo review many times at several levels,

both local and national, and that by dissolving the HGTS it would not make the review any less intense, it would only make the process more efficient by taking out an intermediate step in the review at the national level.

Dr. Gellert noted that no one who had supplied written comments had thought it a good idea to abolish the HGTS and he said he personally did not see much redundancy in the reviews done by the HGTS and the RAC. He noted that the membership of theHGTS provided more specialized expertise to review these protocols and that with its limited role its schedule provided for more in-depth review of them than could be done in light of the already tightly constrained schedule of the RAC. He noted that several written responses had in fact suggested the distinction between the RAC and HGTS be made greater, allowing the HGTS to look into these proposals more on the lines of a study section. He also pointed to the fact that in the past the protocols that had come in would not have been able to be approved without the in-depth technical discussions which the HGTS had undertaken before they were approved. He noted the many revisions that each approved protocol had undergone. He concluded by saying that he would hate to see the HGTS abolished or even weakened at this point because he felt the protocols were not sufficiently routine to be able to be approved without the in-depth discussion of technical issues. However, he said he felt the RAC could consider how to make the workings of the subcommittee moreefficient.Dr. Anderson said that one advantage of the proposal would be to make the RAC the primary body with the ability to make the most informed decision on a human gene therapy protocol. He said at present the subcommittee goes through the technical details and when the protocol comes before the RAC it merely sees a summary of what has happened and is asked to ensure that any questions posed by the subcommittee are answered. He said he did not believe that the RAC is making the kind of informed decision that it could and should be making on these protocols.

Dr. Walters noted that of the 11 letters whichORDA had received relative to this proposal, 3 came from members who currently served on both the RAC and theHGTS, 3 came from members of the subcommittee who were formerly RAC members, 4 came from members of the subcommittee who had never been RAC members, and one came from the Director of the Committee for Responsible Genetics. He noted that they unanimously opposed abolishing the HGTS. Further, a twelfth letter had come from Dr. Miller of the FDA which took the opposite view.

Dr. Walters said the eleven letters opposing the abolishment of theHGTS put forward three main arguments:

1. Local review committees often lack the relevant expertise to evaluate human gene transfer and human gene therapy protocols;

2. To date, the HGTS has identified problems in protocols and requested additional data that in fact have led to important revisions in the protocols and requested additional data that, in fact, have led to important revisions in the protocols or supplements to the protocols which have allowed the RAC to approve the protocols the first time they had come before the RAC in light of these clarifications and additional data; and,
3. The existing review process has won the confidence of both the general public and political leaders.

Further, Dr. Walters added the following two arguments for maintaining theHGTS:

1. If the subcommittee were abolished the RAC would lose ready access to the expertise of several highly respected scientists and ethicists who are currently rotating off the RAC; and,

2. The RAC is currently in the process of reviewing and defining its future role, and that only after this process is complete should the role of the subcommittee be addressed and, if necessary, modified.

Dr. Walters then commented on the letter of Dr. Miller from the FDA. He noted that from the beginning the duplicity of review was evident, but that this was a conscious decision on the part of the RAC so as to ensure a public review process under the auspices of NIH.

Dr. Walters said that Dr. Kelley's letter proposed a "study section model" for the subcommittee and that he agreed in part with this concept. However, he said he felt that the technical expertise in the science must be present on the subcommittee in order for the review to be credible and that he felt the subcommittee must provide an initial review of not only the technical aspects of the proposals, but a thorough look at the ethical considerations.

Dr. Walters said that for these reasons he disagreed with Dr. Anderson's proposal, but that he agreed that the RAC should look at this again in a year to evaluate whether the role of the subcommittee is continuing to be fruitful and constructive.

Dr. R. Murray then discussed this history of this proposal from the standpoint of the *ad hoc* committee which had been convened to look into the comments received during the public hearings undertaken by the RAC, at which this issue was first discussed. He said that he did not consider this proposal to be without merit but that it was perhaps premature in light of the ongoing process of evaluating the role of the RAC for the future. He noted that by having the dual role it allowed him to more readily deal with the patient concerns and ethical issues which he was concerned with, without having the intense discussion of the technical issues of the protocol being discussed at the same time. He summarized by saying he felt that the role of the RAC should be clarified before any decisions could be made relative to abolishing the HGTS.

Dr. Kelley said he agreed with the concept of having a national review of the technical issues surrounding human gene therapy protocols, however he noted that it was clear that the rate of submission of these protocols would increase dramatically in the future and that this should be taken into account in these deliberations. He outlined the process of study section peer review which the NIH has used to help in making funding decisions on research grants and noted that it provided a detailed review by experts which he felt should be mirrored by the HGTS. He said that he felt the HGTS review should be more like that done by study sections and that with increases in both technical expertise as well as ethicists familiar with the area that this could be accomplished with minimal change in the subcommittee structure. He added that he would like to see the subcommittee assign a priority score to each proposal with the aim of eventually developing a funding mechanism for this research. He said this could be accomplished by means of some sort of a set-aside mechanism or by high program relevance, but he wished to see the association of a priority score and funding mechanism being brought to bear on each application.

Dr. Kelley said that ideally he would like to see the RAC continue to act much in the same way the

national advisory councils do, making sure that there is broad representation of the public interest and expertise across a wide range so that there will continue to be public review at the national level for these protocols. He said that he thought Dr. Anderson's proposal was appropriate insofar as questioning the current workings of the HGTS and the RAC. He said that currently there is a lot of interest in the field and he believe that this kind of thinking could be brought to bear and used to support the discipline as the field develops.

Dr. McGarrity noted that there were some differences in what was currently being done versus the "study section model," the major one being that study sections really only deal with reviewing extramural grant proposals, while the HGTS is looking at proposals from the intramural NIH community and privately financed studies as well. Further, he asked what the threshold would be for a proposal to move from the HGTS to the RAC for review.

Dr. Wivel noted that in the current NIH system the study sections do not service one institute, but rather review proposals in a given area of expertise for many institutes and the funding body is the institute council. Therefore if the HGTS were to review a protocol it would be forwarded to the relevant categorical institute, center or division (ICD) for funding, leaving no role for the RAC in this process, since it is not a council and does not have funding authority.

Dr. B. Murray said she found it interesting that members of the RAC who had never been on the subcommittee did not submit written responses to Dr. Anderson's proposal. She said she felt at a disadvantage in having to act on proposals which were already in a pre-approved state and where the attitude was to rush these protocols through since they had already received a technical review by the HGTS. She said she envisioned at some point that one committee or the other should subsume the responsibilities of the other but that there be a single committee in which no less rigorous review would be given and where less duplication would take place in the overall review of human gene therapy protocols. She did note that by having the subcommittee it allowed ORDA to continue to use the expertise which otherwise would drop by the wayside as members rotate off the RAC or the HGTS, but that she felt this could be accomplished by appointing *ad hoc* members to whatever committee evolves from this process.

Dr. Anderson said he agreed with Dr. Kelley's comments insofar as getting a study section started to look at human gene therapy proposals because he felt the time had come for such a study section. However, he said he thought that the subcommittee was not the mechanism to do this in so much as the RAC and HGTS are already under criticism as being regulatory in nature and NIH does not have a regulatory responsibility and this would only further complicate this issue and he felt it would never be allowed to happen. He also noted that his purpose in presenting this proposal was to get the committee to begin to look at the role of the subcommittee and to begin to discuss what its future role should be, and he noted that he felt this was what was in fact happening during this discussion.

Dr. R. Murray said he would oppose the "study section model," because he felt it would do nothing to solve the problem Dr. B. Murray raised about the committee members not feeling fully informed. He noted that advisory councils have more things to do and less time for review of proposals than the RAC and if the "study section model" were followed there would be even less review in the RAC than is now taking place. Secondly, he added that the study sections do not allow for the interface with the investigators which takes place at both the HGTS and the RAC, and he added that he found this refreshing and enlightening to have the investigators present to defend their protocols and that it was an educational process which improved everyone's knowledge of the field and where the field is going.

Dr. McGarrity underlined the fact that the Charter of the RAC also states that meetings will be held in public, and noted that this differs from the standard review of grant proposals by study sections.

Dr. Schaechter agreed with the comments of Drs. B. Murray and R. Murray and noted that down the road an avalanche of human gene therapy protocols was coming and that it was important to look at these issues without having a mission orientation and to stay away from trying to prioritize protocols, but rather to simply evaluate the scientific, human and societal qualities of the work being done.

Dr. Henry Miller spoke in favor of Dr. Anderson's proposal and said that he felt the best aspects of both committees be extracted and merged into one committee to arrive at a single mechanism with a primary concern in this area.

Dr. McIvor said he was in favor of staying with the current mechanism, despite being in favor of having a new funding mechanism for human gene therapy protocols. He said he felt the current mechanism works well and is able to closely scrutinize these protocols from all angles. He said he felt the role of the RAC and the HGTS was to gain an initial awareness of the issues involved in human gene therapy and to address them as best as possible. Because this is a new area of science the ability of the committees to address the science is sometimes made difficult but he said he felt that by conditionally approving protocols after initial review and allowing the investigators to supply additional information and make revisions to their proposals this has allowed the subcommittee and the committee to work very well as a mechanism to identify problem areas and scrutinize the work being undertaken.

Ms. Buc asked whether there was a means by which a protocol could get to the RAC without being approved by the HGTS. Dr. Wivel said protocols must first be provisionally approved by the HGTS before coming to the RAC. However, Dr. Anderson amplified this by noting that there is a procedure whereby if there are two straight deferrals of a protocol by the HGTS the investigator may appeal directly to the RAC for approval.

Dr. McGarrity asked Dr. Ledley how he felt about the process, having just undergone the review process. Dr. Ledley said he felt the two-step process was a good one and that it focused the investigators' attention, thoughts and planning on the most critical issues involved in the protocol. He said he favored the approach being taken by the RAC whereby the investigator is present at the initial critique, rather than the study section model in which the investigator receives a "pink sheet" at some later date and does not have the ability to interface with the reviewers.

Dr. Post expressed the opinion that he would like to have more information on the initial review before the RAC met to discuss a protocol. He said he felt there should be a mechanism short of abolishing the subcommittee to give early feedback to the investigator as well as providing some detailed review for the RAC on proposals considered by the subcommittee. He also said he felt that as human gene therapy protocols become more routine and the numbers submitted for review increase that it is important for the RAC and the subcommittee to think in terms of what their proper role is in the review of these protocols in order to expedite the process while maintaining a high standard of review.

Dr. Walters said that he felt this discussion was fruitful insofar as he had not viewed this process from the standpoint of a member of the RAC who was not on the subcommittee. He said that perhaps some combination of the parent committee and the subcommittee which met perhaps six times a year might be required in order to keep up with the volume of proposals which are likely to be submitted in the future.

Dr. Walters said that he felt the last meeting of the subcommittee was one of the best they had in terms of review from both the technical and ethical standpoints and he said he was stunned when shortly thereafter he received the memorandum from Dr. Anderson which outlined his proposal to abolish the HGTS.

Dr. Kelley said that as long as the two committees have different functions it is inevitable that one should be more informed than the other. He said that otherwise the process would be redundant. He said he felt more scientific expertise was needed on the HGTS as the numbers of protocols coming before it increases.

Dr. Atlas said that being asked to review a protocol and not having the minutes of the subcommittee review leads to ambiguity and that he felt a mechanism was necessary for being able to have this information available to the reviewers. Further he said he was concerned that when lay people and the public are asked to serve a role on the committee that they not be totally indoctrinated by their scientific colleagues and therefore the role of the subcommittee should continue to be aimed at a more technical approach to the review of these protocols and that a somewhat different review be undertaken by the RAC which would encompass the public viewpoint as well as the detailed scientific protocol review which has taken place in the subcommittee.

Dr. Gellert suggested that the minutes of the subcommittee be circulated to the members of the RAC before each meeting so that they could be used as a refresher as to the issues considered by the subcommittee. Dr. Wivel noted that when the meetings are only 4-6 weeks apart this provides a problem for being able to obtain the minutes for these meetings in time for the RAC meeting. He suggested that the unedited transcripts could be provided, but noted that they were quite lengthy. Dr Walters said he felt that the RAC reviewers should be provided those sections of the transcripts which pertain to the protocol that they are assigned to review if they were unable to attend the subcommittee meeting. Dr. McIvor said that perhaps the person who did the review at the subcommittee meeting could provide a synopsis of his review for the RAC reviewers in the form of a single-page letter.

Dr. McGarrity noted that a more taxing problem for the reviewers is the last minute submission of information on protocols which often times arrives right up to the morning of the RAC meeting. He asked if there should be a deadline put in place for materials coming in for the RAC meeting. Dr. Anderson said he was not in favor of such a deadline because in many cases it would mean that the reviews would take place without having the most current data available for review. Dr. Gellert said that he felt that by having data coming in until the last minute made it difficult to write reviews beforehand and that he felt there should be some time set beyond which the information would not be considered.

Ms. Buc said there were disadvantages to setting a deadline. One was that important scientific information may not be available in time. Secondly, it puts investigators who are geographically more distant from the NIH at a disadvantage. Thirdly, if a deadline were to be set the committee would oftentimes have to spend time deciding whether to enforce the deadline when important information comes to light after the deadline.

Dr. Anderson said he felt that the investigators understood this problem and he called attention to the fact that no new information had been supplied to either committee except for information directly pertaining to stipulations put down by the HGTS.

Dr. Schaechter suggested a one week cut-off for submission of data prior to a RAC meeting. There was general agreement on this issue. Dr. McGarrity said that he wanted to raise other general policy issues for the future which could be addressed and asked for comment from the committee. Mr. Mannix said he believed the RAC had passed a motion to schedule a special meeting for a discussion of these issues. Dr. Wivel said the RAC had considered such a meeting, possibly in the form a retreat, and asked for guidance from the committee on when members felt their schedules would allow for such a meeting.

Dr. McGarrity suggested that 3-4 members be asked to begin to formulate a long-range plan for the committee, looking at perhaps a 3-5 year period for strategic planning purposes. Dr.Schaechter said he felt it was important to have NIH involvement in this process as well. Dr. Wivel noted that the Director of NIH had an advisory committee which meets on an as-needed basis and he suggested that this may be a legitimate issue for that committee to discuss and formulate a series of recommendations that the RAC could then take up as action items.

Dr. Anderson said he felt the purpose of his proposed amendment had been well served by the discussion. He apologized to Dr. Walters for not having informed him of his proposal in person. He noted that the proposed amendment had been written before the last subcommittee meeting and he underlined his regrets for not having informed Dr. Walters of his intentions at that time.

Dr. McGarrity said he felt the spirit of the proposal was not meant to be any kind of criticism, but that it document meant to stimulate thinking on the part of the committee as to its role and the role of the subcommittee for the future, and he thanked Dr. Anderson for bringing these issues to light.

There being no further discussion, at this point Dr. McGarrity adjourned the committee and asked them to reconvene at 9:00 a.m., the next morning.

9:00 a.m., May 31, 1991:

Dr. McGarrity called the committee to order at 9:00 a.m. He presented a certificate of service to Mr. Brewer, who had not been attendance on May 30, and thanked him for his service on the committee

Dr. McGarrity noted that because of a mix-up in scheduling consideration of Dr. Brenner's protocol would be delayed and asked Dr. Deisseroth to present his proposal to begin the morning session.

X. PROPOSED ADDITION TO APPENDIX D OF THE *NIH GUIDELINES* **REGARD ING A HUMAN GENE TRANSFER PROTOCOL ENTITLED** *AUTOLOGOUS TRANSPLANTATION FOR CHRONIC MYELOGENOUS LEUKEMIA: RETROVIR AL MARKING TO DISCRIMINATE BETWEEN RELAPSES ARISING FROM RESIDUAL SYSTEM DISEASE VERSUS RESIDUAL CONTAMINATION OF AUTOLOGOUS MARROW***:**

Dr. Deisseroth noted that chronic myelogenous leukemia was a disease in which a very indolent initial presentation evolves into fulminant acute leukemia in which the patients die of bleeding and infection. He said that currently there are three therapeutic approaches to the treatment of this disease, two of which involve bone marrow transplantation (BMT). He noted that the protocol will attempt to control the last phase of the diseased where patients face a 100 percent threat of mortality due to the fulminant acute leukemia and where currently intensive drug therapy is utilized which requires hematopoietic reconstitu tion by means of either an autologous or allogeneic bone marrow transplant. He said the protocol was aimed at trying to determine, in relapse, whether the relapse is arising from residually contaminated autologous marrow or residual systemic disease in the patient.

Dr. Deisseroth said that the dilemma in trying to improve therapy to prevent relapse is that if they are to increase the radiation and chemotherapy to eradicate residual systemic disease there would be increased mortality and if they try to increase the methods used to clean up the marrow this could result in failure of engraftment as well as delayed recovery.

He said the current approach is to use conventional dose combination chemotherapy to reduce the level of contamination of leukemic cells in the marrow and then to collect the marrow at this state of minimal disease and infuse the autologous marrow. However, total body irradiation and combination chemotherapy is insufficient to eradicate all of the systemic disease and therefore this protocol would be aimed at using the LNL6 marking vector to allow them to discriminate between a relapse caused by inadequate preparative therapy or inadequate purging of the marrow. He said what was envisioned was that after the autologous marrow was collected it would be incubated, *in vitro*, with the LNL6 marking vector and frozen. The major question is whether it is possible to introduce the marking vector into enough cells with leukemic blasts so that after engraftment there would be a substantial probability if relapse occurs from the marrow that these blasts will possess the marking vector. If the marking vector genes are detectable in these blasts then one could conclude that the marrow was inadequately prepared and one should focus on cleaning up the marrow further, and in contrast if no evidence of the retroviral trans genome was found in the leukemic blasts at the time of relapse one could perhaps focus more on the systemic disease.

Dr. Deisseroth said they had presented data at the HGTS to show that they were able to mark the chronic phase chronic myelogenous leukemia (CML) marrow by incubating it with the neo gene vector and testing for G418 resistance. He said the neo gene could be detected in leukemic cells in 10-20% of the exposed cells and that PCR analysis confirmed that the neo gene was carried in 30% of these cells. Therefore he said the overall absolute frequency of cells shown to be neo positive in the chronic phase marrow was 4-5%. He said they went on to look at blast crisis marrow samples since the protocol is aimed at these, and they were able, using the same procedures, to show the same level of acquisition of resistance to G418 in the blast crisis marrow. Furthermore, using a specific messenger RNA marker for leukemic cells they were able by PCR to show that 75-100 percent of the blast colonies expressed the retroviral trans genome. He said the program could be considered feasible and the investigators are in a position to expect the blasts, if they are contributing to relapse from the marrow, would be marked with the retroviral trans genome.

In terms of quantitative data, Dr.Deisseroth said they start out with 2 X 10 cells from a marrow collection. They then concentrate the marrow, resulting in a 5-fold reduction to 4 X 10. Then only 30 percent of this will be used in the marking process, so that reduces the number to 1.2 X 10. Then the marrow is subjected to further concentration to remove myeloid and many of the leukemia cells resulting in a 10-fold reduction down to 1.2 X 10 cells. At the time ofcytogenetic remission the level of leukemic cells would be below 1 in 100, and thus the range of total leukemic blasts that would be stored away would be anywhere between 10,000 and 1 million. Therefore, Dr. Deisseroth said he felt there was ample evidence to suggest that not only can the cells be marked, but they would be able to be detected at the time of relapse. He said the only remaining question was whether they would see marked cells in the marrow or not.

Dr. Deisseroth then turned his attention to what is to be gained from this protocol. He noted that the patients themselves will not stand to gain from this protocol in an immediate sense because they are participating in a therapeutic program to control the blast crisis from which they have a 100% chance of dying and to reduce the level of these leukemic cells within their body so as to produce a state in which they may survive for several years. He underlined that the marking process itself has been

proven not to pose any immediate risk to the patient and he pointed to long-term benefits to society in terms of the increasing use of intensive therapy requiring exogenous hematopoietic reconstitution in more common diseases such as breast cancer. He noted that this will not only help identify origins of relapse, but be helpful in understanding and cleaning up the fractionation process and refining purification of hematopoietic stem cells which is a very important technical obstacle to the application of genetic replacement strategies for inherited diseases.

Dr. Leventhal said she was still unclear as to whether normal blasts would be labeled as well as leukemic blasts. Also she said she felt that the cause of the relapse may come partially from the autologous marrow and partially from residual systemic disease and that there may be a different time course involved for these two actions. She said she would like to see a plan of when tests will be done on the patients and what tests will be performed after the marrow is reinfused. She added that she was concerned about certain definitions in the early stopping rule and requested she be provided with a revised protocol so she could be assured that this was clearly stated and consistent for all patients.

Dr. Leventhal then turned her attention to the informed consent document. She said that in Section Four she didn't feel it was fair to tell the patients that the virus being used for the marking vector was "extensively studied" or that it was being used for "treatment" of patients, since neither of these was correct in her view. She said the paragraph which currently states, "Extensive study of this virus marking procedure has been undertaken in mice, monkeys and humans," should be changed to read:

> "This virus marking procedure has been studied in mice and in monkeys. This same virus, and a virus like it, are now being used in studies in patients here and at other institutions. No adverse effects have been observed in all of this study because the vector is modified so that it cannot cause an infection in the cells of the body. It only marks a small number of blood cells in the autologous marrow."

Dr. R. Murray said he did not have prior problems with the technical aspects of the protocol and he said his review would primarily be directed at the consent form. He said he had a problem with separating the therapeutic aspects of the protocol from the experimental aspects of the protocol. He said he had suggested earlier that the paragraph titled "Alternative Procedures and Treatments" be deleted and a paragraph inserted entitled "Intents of Therapy" where patients could agree to participate in various aspects of the protocol individually. He said it appeared that if the patient signs the form as it now appears that they are agreeing to participate in everything. Furthermore some terms needed to be defined for the patients. He said the term "autologous" could be changed to "your own cells," and the term "drug regimen" made the protocol sound as if it were therapeutic. He also pointed out that he was confused by the meaning of the sentence which states, "The use of marked cells to identify the sources of relapse may be of benefit to patients on future protocols, but this research has only a small chance to be of immediate benefit to you." He said this was confusing and should be clarified. On the whole, he said he felt the revised consent form was better than the original but he said it still needed some refinement. He also noted that Mr. Alexander Capron had reviewed this same protocol and mentioned these same issues in his letter in reference to the consent form.

Dr. McIvor said that he wanted clarification that after culturing these colonies it was impossible to

distinguish between normal and blast colonies, since this is a distinction in this protocol from the AML protocol which was approved at the prior RAC meeting. He said he also wanted to know the percentage transduction rate that has been achieved thus far. He said the presence of BCR-ABL verifies that the colonies are leukemic but that since the investigators also hope that non-leukemic colonies will also be labeled he felt this needed to be based on the presence of something, rather than the absence of the BCR-ABL PCR product. He said this needed to be clarified since the aims of the protocol were twofold: one, to determine source of relapse; and secondly, the extent to which there is stem cell involvement in this process. He said the first aim seemed to be attainable with this protocol but said he felt the committee needed clarification on the second aim. Further, Dr. McIvor said he also would like to know what level of totipotency the investigators were capable of determining in the colonies.

Dr. McIvor suggested that Dr. Deisseroth provide a flow chart of exactly what is going to be done as there are many steps involved in this protocol. And finally, he asked if the colonies could be analyzed microscopically as far as their varying morphology to determine whether they are leukemic or normal in an attempt to provide support for the BCR-ABL PCR data. He said that he felt there was a significant possibility that even though there are leukemic cells in the marrow they will not come up tagged in the relapse material, and thus there is a good chance that the results of the protocol may be uninformative. He said one way of dealing with this would be to keep trying to increase the transduction frequency or attempt to label all of the marrow cells. He said he felt it was important tha both the investigators, as well as the patients, be aware of this possibility that no information at all will be gained from this gene tagging.

Dr. Post said he felt that it was evident from the protocol that there was no doubt that leukemic cells are being given back to the patient in the autologous marrow and that this experiment is only an attempt to figure out which set of leukemic cells is responsible for the relapse. He asked Dr. Deisseroth to comment on this and correct him if this was not the case.

In response to Dr. Leventhal's questions, Dr. Deisseroth said that the critical time for interpreting the experiment and the therapeutic outcome is at the time of relapse. However, on an experimental leve this may not clarify the question, but he said they would also be analyzing marked marrow samples taken from patients incidental to their regularly scheduled clinically-driven evaluations of the marrow to look at the level of leukemic cells as well as any information that can be gathered on the level of the virally marked blasts. He said that at the present time the only technique for doing this is the molecular assay which he had presented. However, he noted they were involved in developing another method to analyze the presence of these retroviral sequences using saturated DNA proves for the neo sequences which will be used to stain a cell so that they can discriminate between normal and leukemic cells on a cell-by-cell basis under the microscope. He said this technique had not been perfected but they will continue to work on it.

As far as the early stopping rules, Dr. Deisseroth said they had not been included in the protocol at this point, but he assured Dr. Leventhal that they would be inserted into the protocol.

In response to Dr. R. Murray's concerns, Dr. Deisseroth said that he agreed that the issues of therapy should be separated from the marking, and what they have done is split away all therapy from the marking protocol and they now have a separate protocol for the therapy which patients will read over and be able to sign an informed consent document on prior to being approached about the marking protocol. He said he purposely left some information about the therapy in the marking protocol because he felt it was important to provide information to the patient on the marking protocol in the context of the therapeutic setting. He underlined that the patient will first sign the

informed consent for the therapy protocol and only after he has signed onto this protocol will he be approached to sign on for the marking protocol. He said that he would remove all reference to therapy, but that he felt this only helped to clarify this document. He agreed that the terms "autologous" and "drug regimen" would be defined and added that he felt this was a constructive suggestion.

Dr. Deisseroth said the reason he had mentioned that this had a "small chance ofbenefitting a particular individual in the future" was that if a patient participates in the marking and the therapeutic program and has a fairly substantial remission in terms of time and then relapses it could be conceivable that information would be available from the study which drive the investigators to subject that patient's marrow to a more stringent purification procedure.

In response to Dr. McIvor's questions, Dr.Deisseroth said that he was correct in stating that there was no way to discriminate between normal and leukemic colonies, in contrast to Dr. Brenner's protocol. But he added that there are molecular assays which are totally specific and done on a colony-by-colony basis that could be employed. He reminded Dr. McIvor that they continue to be headed in the direction of developing a fluorescent *in situ* analysis, as he had alluded to earlier. As far as the scale-up is concerned he said thatGTI would be performing this in Houston and would be supplying the investigators with the FDA-approved viral supernatant.

Dr. McIvor asked what had been done in Dr.Deisseroth's laboratory in terms of scale-up. Dr. Anderson interjected that one would not want to perform a major scale-up for reason of cost, just to say that they can perform it. Dr.Deisseroth said that he did have some marrow frozen away from patients who had expired and said it would be possible to thaw this and expose it, but noted that this would be different than using fresh marrow from a patient and performing the marking.

Dr. McIvor said this would shed light on the issue of anticipated efficacy and said that he would feel more comfortable if such a scale-up could be performed. He said the committee had to make a decision as to whether they anticipate the protocol is actually going to provide some results, and one of the components in that assessment is the frequency of gene transfer. He said this was absolutely necessary since it is the total basis for the information that is anticipated to be generated. He said the committee may want to discuss whether they would want to approve the protocol contingent on these experiments being done, or possibly to defer the protocol pending the receipt of those data.

Dr. Moen said he was not sure how to do such experiments without using the patient's fresh marrow Dr. Deisseroth reiterated that they could usecryopreserved cells and grow colonies out of them. He said it was not a technical problem to do this, and said that it could be done if the committee felt it were important.

It was pointed out that when Dr. Brenner's protocol had come before the committee there had been no such requirement for full scale-up, and Dr. McIvor said he would be comfortable with making this a suggestion, rather than a requirement.

Dr. Deisseroth said that Dr. McIvor also brought up the question of whether the investigators knew whether they were marking normal cells or not. He noted that he had presented data showing the colonies that grew from normal marrow after exposure to the virus were at very low level and the level now of marking in normal cells is a lot lower at the analytical level than it is at the leukemic level. But he said there was no reason to expect that if one were to purify those normal progenitors from normal marrow that it would not be possible to see same frequency of marking. He emphasized

that the immediate objective of the study is not to study normal marrow, but rather to determine the origin of relapse. He said in the next phase of trying to follow the purification of the normal stem cell this would be an objective, but he noted that this was not now before the committee. He said this was of interest to the investigators and that they would continue to address it over the next months and years and when they have collected data relevant to these questions they would return to the RAC with another protocol.

Dr. Deisseroth said he would be happy to, in consonance with Dr. McIvor's suggestion, include a flow chart in the protocol to list the exact sequence of events. He added that they were planning on using quantitative laser confocal microscopy to quantitate the copy number of trans genomes in the cell. He presented a slide depicting the algorithm for interpreting the results of the experiment. He said that clearly one possible outcome of the marking would be that the blasts would be marked at multiple DNA sites and this would indicate that a polyclonal relapse had occurred which probably had arisen from the marrow. However, if the blasts were marked at a single site, that would mean that a single cell had arisen from the marrow which is dominating the relapse population and could have multiple interpretations. He noted that one such possible interpretation would be that a second mutation was acquired following the marking which conferred a selective advantage on this cell, and he felt this would be an interpretable result. However, if none of them are marked, then this would leave the interpretation up in the air. He noted that Dr.Leventhal had suggested that different results may be seen in different patients and he said he agreed with this and that he did not expect to see homogeneous pattern of response in all patients. However, he noted that unless a cell acquires another mutation after marking which gives it a selective advantage over all other cells he would expect to see a polyclonal relapse, provided a sufficient number of cells are in the marrow at the time of marking. So he said he felt there was no way to predict the outcome short of performing the experiment.

Dr. Leventhal suggested doing a marrow at one week would allow the investigators to find out if their whole technical set-up had worked and at least give them the knowledge that they were able to reinfuse the cells and find them. She said this would be a lot to know in terms of interpreting later results.

Dr. Deisseroth agreed with her and said that in fact he planned on doing this. He added that he would include an algorithm in the protocol which would be specifically directed at all the time points at which measurements would be done.

Dr. Krogstad asked what was projected to be necessary to answer the question of the site of relapse in terms of numbers of patients and projected time and expense. Dr.Deisseroth said that they had undertaken an analysis of this question from a quantitative standpoint and that basically there are as few as 10,000 up to as many as a million marked leukemic cells in the marrow and as many as 4 X 10 nucleated cells. However, there are so many variables that contribute to the repopulation with marked leukemic cells competing with other cells that all that can be said at present is that cells can be marked. The estimated numbers are sufficient to give an expectation that under conditions of reconstitution there is a reasonable probability of a polyclonal relapse occurring from the marrow, but it may also occur from the peripheral blood. However, the redeeming feature of this type of clinical investigation is that the tools are now available to formally address many of the explanations for any given outcome. He noted that a few years ago in this form of leukemia they were limited to light microscopy which lacked sensitivity and specificity, but that now there are molecular assays which are totally specific and possess the ultimate sensitivity, and therefore he felt the time was now right to try to answer many of these questions in the clinical investigative setting.

Dr. Geiduschek said he felt the issue that had been raised regarding the fundamental objective of the study was the source of relapse and he said he felt this was an over-statement of the aims of the study. He said it seemed the problems with that stated fundamental objective were a matter of arithmetic, rather than anything more complicated. He said there was a certain inability to be able to write the equation to confirm the source of relapse and that he felt the fundamental objective was harmed by the possibility of coming up with no outcome because of the inability to determine the source of the relapse.

Dr. Deisseroth said that the reason they want to do the study is to determine what the absolute probability is of there being 10 successive reconstitutions without marking a cell. As far as levels of cells in the marrow and the marking frequency he said that what could be said is that the probability of relapse occurring from the marrow was now technically capable of being detected.

Dr. McIvor said that he thought what was being sought was the statistical analysis of the problem. He said that if the assumption is made that aleukemic cell infused with the marrow has an equal probability of contributing to relapse as a cell that remains in the body, then you need the transduction frequency and based on this transduction frequency and the percentage of cells that are actually contributing to the relapse you can predict the probability of an informative outcome or not. He said this is what was needed to answer the question.

Dr. Deisseroth presented a slide to summarize this. He said that there were somewhere between 10,000 and one million leukemic blasts in the transduced marrow that are marked, and the gene marking rate is 3%, therefore the result of this shows that they are at about the 10% level. However, he stressed that there are many unknown variables to be taken into account and therefore this is the reason for going ahead with the investigation itself. He said there was no way to know what the outcome would be without doing the experiment.

Dr. McGarrity noted that there were still many members who wished to ask questions but that for a number of reasons it was necessary to take the morning coffee break at this point. He asked the committee to reassemble at 10:45 a.m.

Dr. McGarrity called the committee back to order at 10:45 a.m., and noted that during the coffee break Dr. Walters had asked to comment further on the informed consent document. He suggested that these comments should be entertained and that then the committee should try to come to some resolution on this protocol.

Dr. Walters said he felt this informed consent document had done the best job of separating the gene marking study from the underlying therapy of any the committee had thus far seen. He noted that he had spoken with Dr. Murray and Dr.Deisseroth during the break and that he had three suggestions which had been agreed on by all parties:

1. To change the title of the protocol to "Gene Marking of Bone Marrow Cells in Patients with Chronic Myelogenous Leukemia;"

2. Place the paragraph which Dr. R. Murray had commented on relative to the participation in the study being optional and unrelated to the bone marrow transplantation protocol at the very beginning of the consent form so that patient could see and know that they can have the bone marrow transplantation without taking part in the gene marking study; and,

3. Under "Purposes of the Study," to insert a phrase at the beginning of this section which would clarify the aim of the study by stating, "To genetically mark cells in order to identify the origin of relapse."

Dr. McGarrity said he felt the informed consent portion of the protocol had thus been taken care of and noted that he felt the technical algorithms and statistics had also been well described and that they showed that a positive result would be informative, while a negative result would offer no further information.

Dr. Deisseroth said that this issue of the negative result was discussed with a few of the reviewers at the break and that after discussion they had come to the conclusion that if a negative result were obtained it was of more than no value. The probability of a negative outcome being due to an event other than relapse from the systemic circulation is very, very low that this also provides some information.

Dr. Krogstad said that his conclusion was now that it might be reasonable to allow a finite number of patients to be tested and use the results from this finite group to clarify some of the issues brought up in this protocol. He said there were so many unknowns that it would be impossible to move ahead without having some human data.

Dr. Haselkorn added that he felt the protocol should contain positive controls on all samples to rule out the possibility of having no RNA in a sample. Dr. Deisseroth said that this was a good suggestion and in fact is part of the algorithm forPCR analysis.

Dr. Carmen said he had some minor changes in wording in the consent document that he felt were also called for which had not been noted in Dr. Walters' summary. He said the changes were under "Description of Research," paragraph 3, beginning on line 11, to strike out the term "DNA molecule" and insert "a bacterial marker gene" in its place. Then change the sentence in the same paragraph that begins with "Thirty percent of your stored cells..." to read:

"Thirty percent of your stored cells will be mixed with a specially engineered **mouse** virus which cannot cause an infection in the body. **This virus will mark your** cells with **a bacterial gene** that makes it possible to find these cells."

Dr. Deisseroth agreed to make these changes in the informed consent document.

Dr. McIvor said he was not in agreement that a negative result would mean that the relapse was caused by residual systemic leukemic cells. He noted that if 10% of the cells were marked and only 1 cell contributed to the regeneration of a tumor and it all came from the marrow, there was a 90% probability that there will not be any marked cells in the population of relapsed tumor cells. Dr. McIvor asked that the informed consent document state "It is also possible that no information will be gained from the gene marking study." Dr. Deisseroth agreed to include this in the consent form.

Dr. McGarrity asked Dr. Walters to compile a master copy of the changes which were made to the

informed consent document and then asked for a motion on the protocol.

Dr. McIvor moved that the protocol be approved contingent upon the changes in the informed consent document and with the suggestion that a large-scale dry run be attempted before the actual experiment is performed in up to 10 patients. He asked for clarification on the early stopping rule to be employed in the protocol. Dr. Deisseroth said that the usual rule was in therapeutic protocols to stop if there are 3 treatment deaths. In this case, if there were 3 failures to engraft the study would b stopped. He noted that the investigators would have back-up unmarked marrow to cover this contingency and thereby not subject the patients to an adverse outcome in terms of the viral marking on the viability of the marrow.

Dr. R. Murray seconded Dr. McIvor's motion.

Dr. Leventhal asked if Dr. Deisseroth was going to provide a full revised protocol with a road map stating when each step would be done. He said he would send that in immediately.

There being no further discussion, Dr. McGarrity put the motion to a vote. The motion passed by a vote of 19 in favor, none opposed and no abstentions.

Dr. McGarrity then called on Dr. Brenner to present the next agenda item.

XI. PROPOSED ADDITIONS TO APPENDIX D OF THE *NIH GUIDELINES* **REGARDING HUMAN GENE TRANSFER PROTOCOLS ENTITLED** *A PHASE I/II TRIAL OF HIGH-DOSE CARBOPLATIN AND ETOPOSIDE WITH AUTOLOGOUS MARROW SUPPORT FOR TREATMENT OF STAGE D NEUROBLASTOMA IN FIRST REMIS SION: USE OF MARKER GENES TO INVESTIGATE THE BIOLOGY OF MARROW RECONSTITUTION AND THE MECHANISM OF RELAPSE; AND A PHASE II TRIAL OF HIGH-DOSE CARBOPLATIN AND ETOPOSIDE WITH AUTOLOGOUS MARROW SUPPORT FOR TREATMENT OF RELAPSE/REFRACTORY NEUROBLASTOMA WITHOUT APPARENT BONE MARROW INVOLVEMENT: USE OF MARKER GENES TO INVESTIGATE THE BIOLOGY OF MARROW RECONSTITUTION AND THE MECHANISM OF RELAPSE* **:**

Dr. Brenner apologized for not being at the meeting in the morning due to a misunderstanding in meeting location. He said these protocols were similar to those proposed and approved at the last RAC meeting for AML, as well as the protocol of Dr. Deisseroth which was just discussed.

Dr. Brenner said that children who have neuroblastoma who are over the age of one year who go into remission with chemotherapy almost invariably relapse. He said the aim of the study was to try to eradicate the minimal residual disease which causes the relapse by giving them intensive chemotherapy followed by autologous bone marrow transplantation.

He said that previous experience had shown that many of these children subsequently relapse nonetheless and that this may be because the disease was not eradicated in the patient or that the marrow harvested prior to the most intensive chemotherapy contained residual tumor cells which have then repopulated the patient and caused relapse. He said that if it could be determined that the marrow contained these cells, the investigators could undertake a process of purging to remove those cells from the marrow beforereinfusion. He noted that although purging techniques exist for neuroblastoma in marrow it is not known whether malignant cells remain in the marrow or whether the purging techniques currently available actually remove the malignant cells. However, if a technique of purging the marrow could be determined then it would make possible autologous

marrow transplant with a marrow known to be safe and the children could then undergo multiple courses of highly intensive chemotherapy which could eradicate a higher proportion of minimal residual disease and actually start curing a higher proportion of patients.

He said that this was an investigational protocol to some extent, but it was hoped that it could be moved quickly into practice to allow a therapeutic benefit by developing better methods of marrow purging and thereby increasing the possibility of curing a higher proportion of children with advanced disease.

He said he would outline the experimental basis for the protocol and then discuss the clinical relevance and experimental details.

He said it was possible to actually identify neuroblastoma cells grown from the marrows of patients with the disease and they have a very distinctive morphology. They look different from normal hematopoietic cells in that they are larger and have neurofibriles which extend from them. They can also be identified more definitively, *in vitro*, by use of monoclonal antibodies. Secondly, they are able to be marked and grown on selective media. Dr. Brenner said the efficiency of marking is rather lower than in AML, at 1-3%, with a wide variation of 0-14%. This can be confirmed by PCR analysis. He said he was reasonably confident that neuroblastoma colonies growing in selective media could be marked pre-infusion. However, he noted that at the 1-3% transduction efficiency level, the question was whether these could be detected subsequently after relapse in the patient. He said this was contingent upon how many cells were causing the relapse. He said that if only one cell were causing it, there would only be a .3% chance of detecting a marked cell in the patient. However, if hundreds or thousands of cells contributed to the relapse, then there would be about a 95 percent chance of detecting marked cells in the patient. He noted that even with a .1% transduction efficiency level, if 1,000 malignant cells remained behind in the remission marrow, then the investigators would have a 95% chance of detecting a marked relapse within the first 3 patients who relapse.

He said it was important to know how likely it would be that this number of malignant neuroblastoma cells would be left behind in the remission marrow of the patients. He said that by looking at AML in which the ability to detect residual malignant cells is more sophisticated and more sensitive than for neuroblastoma cytogenetic methods only allow for the detection of 2-5% of residual blasts. However, fluorescence microscopy allows the detection of from 1 in 1,000 to 1 in 10,000 malignant cells. This would mean that a 20 kilogram child could still be receiving at least 20,000 blasts in a marrow reinfusion since 100 million marrow cells are infused per kilogram. He said that as more sensitive methods have come into use for detecting minimal residual disease in marrows that are said to have been in remission that when they have been examined retrospectively they have turned out to be in florid relapse. Therefore, he said that it was likely that most of the remission marrows will have a substantial number of contaminating neuroblastoma cells and that a 1-3% transduction efficiency would be adequate to detect in subsequent relapse.

Dr. Brenner said that since as few as 1,000 neuroblastoma cells can be detected in a remission marrow if there is a marked relapse, and since the most sensitive technique now available will detect 1 in 10,000, this technique will allow the investigators to evaluate the efficacy of purging and determine whether or not this risky procedure should be carried out.

Dr. Atlas said that he would first relay the comments of Dr. Kelley to the committee. Dr. Kelley had said that he felt Dr. Brenner had responded to the provisions of the HGTS and, while he was not judging how he would vote after hours of discussion which may ensue, his comments were indeed

favorable.

Turning to his own review, Dr. Atlas said that he was somewhat confused as to whether or not there had been an adequate response to the first provision set down by theHGTS that, in fact, there be further evaluation of the procedures for*in vitro* bone marrow assays to detect residual tumor. He noted that Dr. Brenner did not address this issue in his letter that was sent as a follow-up to the HGTS meeting. He said he would defer to Dr. Walters whether the response to this was adequate.

Dr. Atlas said that with regard to the second provision laid down by theHGTS in regard to the stopping rule that he felt there was some confusion as to which document actually was the one supplied in response to this request. He said his comments would be based on tab 1435. He said he was concerned about the first paragraph which indicates that there is now another procedure under development that may obviate the gene marking and that this would cause the study to be stopped. He said it wasn't clear to him what percent of patients would be treated with this new procedure and whether it was sensitive enough to determine that the gene marking protocol was not necessary.

Dr. Atlas said there were also problems with the informed consent document. First, he said he was not convinced that the form would be intelligible to a child of 7 years of age. Further, he wanted to know how some of the information would be used, in particular studies which are to be done before treatment. He said it was unclear whether these results would be used as entrance criteria and further whether the patient would be notified of the findings resulting from these studies. Further, he noted there were typographical errors in the document.

Dr. Atlas commented that he felt this consent form had the same problem as many others that had been reviewed to date in that it failed to separate the separate the alternate procedures that are potentially therapeutic from the gene marking procedure which has a negligible chance of providing any therapeutic value to the patients. He said there was a need to separate these issues of therapy from issues of research. Finally, in the consent form, he noted that paragraph 8 was the only time th phrase "my child's care" is missing in descriptions of what is to be undertaken and he said he assumed this was a typographical error and said he believed it should be corrected to the standardized form of "my (my child's) care."

Mr. Brewer said his concerns were mainly with the consent form and that Dr. Atlas had covered mos of them. He said there was a general question of formatting which he believed needed to be discussed. He suggested that the logical flow of the document was not very good and suggested the investigators use the examples from Pittsburgh and M.D. Anderson as models to follow, provided their local institutional committees had no problems with this.

Secondly, Mr. Brewer said that clearly there are different risks involved in the therapeutic portions of the study than there are in the gene marking portions and he said he felt these should be kept separate for clarity. He also suggested adding a sentence, as in Dr.Deisseroth's protocol, relative to the fact that a negative result may not result in any useful information being gained. He said that in consent forms which had been reviewed in the past there was a statement which recognized that no monetary payment would be made in the event of physical injury or illness while on the protocol which required amending to state that this was only the case for non-negligent injury or illness. He said this should be corrected to read likewise in this case. He also questioned who made the determination in the event of injury or illness who made the decision as to what constituted necessary medical treatment. He said this should be clarified.

Mr. Brewer added that the use of the term "cure" was altogether too definitive and that perhaps it should be replaced by something along the lines of "the best medically indicated treatment." He said that in the discussion of the risks there was no reference to adverse effects on antibiotic therapies and said he felt it should be made clear to the patients that this procedure may in fact weaken the effects of such therapies.

Mr. Brewer noted that the introduction and summary were confusing to him and he had made an effort to roughly rewrite these sections. He said, however, that since he was a lay person that it should not be held to be a requirement that the protocol be revised in this respect and he offered it to Dr. Brenner for his use.

Ms. Buc said the assent document stated the following: "You will also receive a total of eight bone aspirates." She said this should be put into language understandable to a child.

Dr. McIvor said the protocol was, in fact, subject to the same limitations in terms of coming up with informative results as the other protocols which had been addressed at today's meeting. He asked what was known about what might be contributing to tumor relapse in neuroblastoma and asked if there had been any studies in animals looking at this issue. He specifically was interested in knowing how many cells were necessary in order to form a tumor in an experimental system and if anything had ever been tried to determine the clonality.

Dr. Krogstad said he felt many of the questions which were being asked would not be answered during this discussion, but only through performing experiments, and he said he hoped that in the future the investigators carrying out this research will update the committee on what their evolving information is concerning these topics which are heavily debated during these meetings.

Dr. McGarrity noted that as part of the approval process all investigators are asked to update the RAC as to the progress on their protocols at least once every six months.
Dr. Anderson noted that they had been giving updates at each meeting of both the HGTS and the RAC since their protocols had been approved and said he felt there was no problem in continuing this process. Dr. McGarrity noted that with the increased number of protocols and the increasing number of investigators who are not geographically located in the Washington, D.C. metropolitan area, that perhaps consideration should be given to written short reports rather than oral reports before the RAC and HGTS.

Dr. McGarrity then asked Dr. Brenner to respond to the comments of the reviewers. Dr. Brenner said that as far as his responses to the provisions laid down by the HGTS, he felt the answer to their first provision was found in Appendix E, which describes how the investigators plan to analyze the marrow and determine whether it contains relapsed cells. He continued by saying that there is no method currently that will allow investigators to know that the marrow is going to cause a relapse and all that can be said is that some marrows are likely to be contaminated. However, it is impossible to know whether those contaminating cells are clonogenic or not, or whether they are end-stage cells incapable of proliferation. He noted that there is an *in vitro* technique under development which will allow investigators to determine whether the patient will develop a marked relapse, and if this becomes available the investigators will be able to avoid carrying out the marking of the cells. This was the premise underlying the stopping rule which had been mentioned previously.

Dr. Leventhal said that at present the *in vitro* cultures were state-of-the-art for the treatment of neuroblastoma, however the results are not received until after the marrow is reinfused. She

underlined that this was not any different than standard experimental clinical practice in these patients at this time.

In response to Dr. Atlas' question about the pre-treatment studies, Dr. Brenner said that these tests would help investigators to assess risk and if such conditions were found the patient would be notified that they may be at increased risk by undergoing the protocol. He noted that if HIV were found the patient would not be transplanted because of the difficulty involved with doing a transplant on an immunosuppressed host. He said he would add a phrase in the informed consent document to state: "We will discuss these altered risks with you (your child)."

He noted, in response to the question referring to the language difficulty in the assent and consent forms, that the Medical Editing Department had revised these forms to conform with the reading comprehension level of 8-10 year olds. He did say he agreed that some of the language was still very complex and agreed to have them reassess this. He also said he would try to separate the experimental and therapeutic benefits although some of these children were expected to go on to participate in subsequent protocols. He said that at least they would add in a sentence noting that the gene marking may not work, as well as some note of the fact that antibiotic therapy may require some adjustment. He said the word "cure" had been purposely put into the document because a proportion of patients do become long-term survivors and are apparently cured. He said he would modify this wording but he felt that there was a hope that at least some of the patients would be long-term survivors and for all intent and purposes cured of theirneuroblastoma.

Dr. Brenner said that the question of who decides what is necessary care is a part of a list of 10 phrases and questions derived from an NIH document and which had appeared in all protocols developed by his institution. He said that as a rule the provision of care was liberally administered and that if there were any question or doubt about the care being given to any patient that the investigators would wish to see the patients and will have an opportunity since there is a plan to follow these patients up for a long period.

Dr. Brenner said that animal data was unclear as to whetherneuroblastoma was the result of a single cell or many cells and he said this was also the case in human cell lines. He noted that he was disappointed with the way in which human neuroblastoma cell lines reflect the behavior of the tumor. He said that cloning efficiencies vary widely and that different cell lines show different adhesion molecules and respond in a varied manner to growth factors. He said the wide range of transduction efficiencies (0-14%) was a clear reflection of this fact.

Dr. Leventhal noted that it was unclear as to how many bone marrow biopsies would be performed and stressed that she felt it was necessary to know the morphology on each biopsy. She said the procedures for bone marrow biopsy needed to be more clearly spelled out in the document. Dr. Walters suggested the investigators separate the consent form for the bone marrow transplant patients from the consent for the gene marking, and if this were done suggested using Dr. Deisseroth's model of a consent form. Dr. Brenner said this was acceptable to him and that he felt this should then be done for the AML protocol as well.

Dr. Geiduschek asked if it was known if there was zero clonality in the multi-cell population which is amplified during relapse. Dr. Brenner said that the basic assumption that is being made is that all the cells grow equally and that having a retroviral marker will neither favor nor hinder subsequent growth and that all cells that are clonigenic would be marked in the same proportion in the patients.

Dr. McIvor said that he wanted to know if there were animal models foneuroblastoma that had been

studied which looked at the issue of the range of cell doses that are necessary in order to generate tumor relapse. He said he felt this information should be available.

Dr. Brenner noted that between 1,000 and 1 million human neuroblastoma cells are sufficient to produce tumors in SCID mice, a strain that has a severe immune deficiency. He noted that it was hard to interpret and said he was not convinced that this data had any relevance to fresh tumors since they are biologically different.

Dr. Leventhal asked what would be done if the patient relapsed somewhere other than in the marrow. Dr. Brenner replied that if it wasn't clinically indicated for diagnosis that a biopsy would not be done simply to address the gene marking question.

Dr. Hirano asked who would bear the cost of these treatments and said this should be stated clearly in the consent form. Dr. Brenner said that since St.Judes was a charitable institution and no patients are charged for any procedures, that this was not an issue. He noted that StJudes even pays for airline tickets and hotel accommodations for the parents of the children.

Dr. Carmen said that in the section entitled "Marrow Harvest and Marking" the term "gene" should be amplified by the use of the word "bacterial" to show that the marking gene is a "bacterial marking gene" in all cases. Dr. Brenner said he would make this change.

It was agreed that Dr. Walters and Mr. Brewer would review the consent form at a later date to ensure that all the revisions had been properly made, since they had been agreed upon by Dr. Brenner and all that was needed was an assurance they had all been accomplished.

Dr. Krogstad moved for approval of the proposals, pending the changes as described in the previous discussions. Dr. Gellert seconded the motion. There being no further discussion, the Chair put the motion to a vote. The motion passed unanimously by a vote of 19 in favor, none opposed and no abstentions.

Dr. McGarrity then called on Dr. Hirano to present the next item on the agenda.

XII. PROPOSED AMENDMENT TO SECTION I-C-2 AND DELETION OF SECTION III-A-2 OF THE *NIH GUIDELINES* REGARDING DELIBERATE RELEASE:

Dr. Hirano said the two arguments that have been put forward frequently in favor of the proposal that the RAC and the *NIH Guidelines* eliminate wording related to deliberate release are:

1. That the RAC has not reviewed an experiment of this type for several years; and,

2. That experiments of this type are currently being reviewed within the framework of existing regulations by other Federal agencies, notably the EPA and USDA/APHIS.

She said that careful consideration needed to be given to this issue in order to avoid a gap in oversight of experiments involving recombinant organisms if these sections relevant to deliberate release are removed from the *NIH Guidelines*. She noted that the "Coordinated Framework for

Regulation of Biotechnology" was still not in place and that EPA and USDA/APHIS were really concerned with commercial applications of the technology and that since some experiments are looking at basic ecological questions which may not involve a plant pathogen, there would still be a gap in oversight for these types of experiments if the *NIH Guidelines* were amended to remove these sections dealing with deliberate release. Also she noted that experiments performed abroad are also covered by the *NIH Guidelines* under two circumstances:

1. If they are supported byNIH funds; and,

2. If they involve deliberate release into the environment or testing in humans.

Furthermore, she noted that paragraph III-A-2 requires RAC review,NIH approval and IBC approval before initiation of an experiment involving deliberate release into the environment of any organism containing recombinant DNA, except for certain classes described in Appendix L. She said removal of III-A-2 could be interpreted as meaning that these experiments no longer require IBC approval, and thus a void in the oversight process would be created. She said that despite the progress that has been made in oversight by other Federal agencies, that until there is assurance that some agency will be responsible for review and oversight of these experiments that the wording should not be withdrawn from the *NIH Guidelines*.

Dr. McGarrity called on Dr. Wivel for his comments. Dr.Wivel noted that Section III-A of the *NIH Guidelines* describes the four triggers for national review which includes experiments involving both human gene therapy as well as deliberate release into the environment. He said removal of the deliberate release experiments from this section would not preclude the review of environmental release experiments by a local IBC. He noted that this was covered in Appendices P and Q of the *NIH Guidelines*. He said this would simply result in the trigger for RAC review being removed.

Dr. Hirano asked where Appendices P and Q were in the *NIH Guidelines*. Dr. Wivel explained that these appendices had been completed and approved by the RAC, however an environmental assessment had still to be completed before they could be officially included in the *NIH Guidelines*, but that investigators are provided with these appendices and advised that they are to be viewed as guidance for the investigators although they are not included in the formal document yet.

Dr. Hirano said she had spoken with her local IBC relative to this issue and that they said they would be concerned if RAC removed itself from this arena completely insofar as they rely on the RAC as a "safety net" for their deliberations.

Dr. Krogstad said that he had originally felt in favor of the proposal, however that he felt Dr. Hirano's points were valid. He said on one hand he felt the trend has been away from RAC review of these proposals, however what was needed was a practical way to remove RAC from the process without leaving a void in the review process and he said he thought this is the process which needed to be addressed.

Dr. Haselkorn said he had no difficulty with the proposed amendments since 99.9 percent of the cases are outside the purview of the RAC at this time and most were of an industrial nature. Further, he noted that there had been no cases of harm to the environment from any experiments conducted thus far.

Dr. McGarrity called on Dr. Sue Tolin from the USDA for her comments. She said it was the position of the USDA that ultimately RAC should not be in the business of reviewing experiments dealing with release into the environment and she noted they had been actively seeking a mechanism to supply guidance to investigators, whether in academic institutions or in industry, but that this mechanism is not yet in place. She noted that USDA was actively involved in formulating Appendices P and Q, but noted that even they did not cover planned introductions outside of a controlled environment with the exception of at the lowest levels in animals.

Dr. Tolin said she favored deletion of the particular clauses called for in this proposal but that she envisioned two problems:

1. Section I-C refers to experiments abroad and that EPA and USDA/APHIS has no jurisdiction abroad; and,

2. Section III-A-1 states that "If experiments in this category are submitted to another Federal agency the RAC will not review them," and this would then remove the requirement for experiments not reviewed by another Federal agency to obtain RAC approval.

Therefore, if paragraph III-A-2 is removed from the *NIH Guidelines*, all that would be required would be the prior approval of the local IBC. Further, this would apply to all organisms now listed as exempt under the *NIH Guidelines* and that this would cause such experiments to not even be reviewed by the local IBCs. She said she was not sure that this is what was intended by the proposals.

In conclusion, Dr. Tolin noted that the USDA Guidelines were published for comment in February and the comment period closed on April 2, 1991. She said the AGRAC had just met and had received 70 comments on those guidelines and she expected revisions would have to be made and republished for comment at some future date. She was unsure of a target date for implementation of the USDA Guidelines but noted that USDA was collaborating and coordinating with other regulatory agencies in this respect as well.

Dr. Henry Miller of the Food and Drug Administration (FDA) said that he thought the AGRAC Guidelines lacked regulatory requirements and teeth because of lack of sanctions for violation. Further, he said that continued NIH involvement in deliberate release experiments was not necessary, not sufficient, and confounded the ability of regulatory agencies to carve out categorical exemptions from what needs to be dealt with on a case-by-case basis. He urged the RAC to approve the proposal to delete these paragraphs from the *NIH Guidelines*.

Dr. McGarrity gave a brief historical outline of the issue of deliberate release as it was viewed by the RAC over the years. He noted that the USDA had developed their guidelines with the aim of dovetailing with the *NIH Guidelines*. He said the committee should take a serious view of their role as being advisory to the NIH Director and that the real issue was whether a void would be created in oversight by removal of these paragraphs. Furthermore, he noted that the RAC had not reviewed an environmental release protocol since 1984.

Dr. Wivel underlined the fact that the removal of these paragraphs would not in any way affect the

way which local IBCs deal with environmental release and the fact that the RAC does not see the proposals is a reflection of the structure which has been developed for a decentralized system of review of these protocols.

Dr. Post asked what would happen if the RAC no longer had responsibility for review and an IBC had a problem with review of a proposal. He asked if the AGRAC was properly constituted to deal with such situations. Dr. Tolin responded by saying that the AGRAC had in fact had a situation come up in which an experiment did fall through the crack as far as review was concerned and that the research agency sponsoring the research provided an environmental assessment so the experiment could be done. She said it was clear from this case that IBCs are not yet totally comfortable in making approvals without better guidance from the Federal Government and she said this was one of the aims of AGRAC.

Ms. Buc suggested a compromise might be to delete the requirement that such experiments come to the RAC, but leave the possibility in place for RAC deliberation on them if requested.
Dr. Doi noted that from an IBC viewpoint it is felt that USDA is the proper place to review these proposals since they have more experience with the kinds of issues being faced in agriculture. He said he felt that once the USDA Guidelines are in place the AGRAC will be a much better place to review environmental release experiments.

Dr. Atlas commented that he felt the EPA and USDA were the proper agencies to deal with the issues of environmental release once they get their procedures and review structures in place. However, he noted that this still left the issue of foreign experiments done with NIH funds open, and in fact seemed to leave the local IBC as the only group judging whether a project funded by NIH and undertaking an environmental release in a foreign country should be approved. He said he felt it was a disservice to the Director of NIH to be removing the RAC from this oversight role.

Dr. Wivel said that the United States participates actively in the OECD meeting in Europe and that the current climate in Europe is for stronger regulatory procedures than in the United States and therefore the likelihood of vigorous review and more restrictions being placed on investigators than in the U.S.

Dr. McGarrity also noted that paragraph I-C of the *NIH Guidelines* states:

> "The Guidelines are applicable to projects done abroad if they are supported by NIH funds."

Therefore, any project done, for any purpose, involving recombinant DNA in any way funded by the NIH would fall under the jurisdiction of the *NIH Guidelines*, regardless of whether the sections proposed for removal are in the document or not.

Dr. Krogstad asked Dr. Wivel to comment on the issue of deliberate release in third world countries where it could be expected to be more likely to take place in order to develop new crops and where there is less history and tradition of regulation. Dr. Wivel said that there is a group of third world countries who are drafting a "Code of Conduct" for environmental release experiments, and he said there is sufficient distrust in the third world that they are doing this totally separate, rather than as part of any other recognized international groups.

Dr. Leventhal asked that if the AGRAC was better able to deal with these issues because of greater expertise, whether they could not simply be dropped from the *NIH Guidelines* and a note sent to the AGRAC to make sure that the categories of experiments now covered in the *NIH Guidelines* be included in the USDA Guidelines? Dr. Tolin said the only problem with this was that they could not have oversight over experiments which are not funded by USDA. Therefore they could not require review of NIH-funded deliberate release experiments.

Dr. Atlas said he felt a crucial issue was the trigger for national review could be deleted while maintaining the ability for an IBC to send a protocol forward which it was not able to deal with for some reason and still expect it to be reviewed by the RAC. Dr. Wivel said that not only could they do this, but in fact, they frequently write in asking guidance from the RAC which is normally supplied by ORDA without bothering the RAC. He said the removal of these paragraphs would in no way affect this ability to consult and, indeed, request RAC review of a protocol by a local IBC.

Dr. Carmen brought up the issue of regulation of transgenic animals. Dr. Tolin said that if recombinant DNA were involved the *NIH Guidelines* would apply. Dr. Miller noted that there were other ways to make transgenic animals, without using recombinant DNA and that these are not covered by the *NIH Guidelines*. Dr. Carmen asked if the RAC were not a suitable forum to review such experiments because of the traditionally ethical, humanistic manner in which it has viewed recombinant DNA research. He asked Dr. Wivel to comment on the situation in which an experiment was being proposed which would fall under the *NIH Guidelines* and whether the RAC would feel that since another Federal agency was reviewing it that may not have the same expertise, it should be reviewed by the RAC. Dr. Wivel said the question would really be one of risk assessment, level of risk and level of containment needed to negate the level of risk.

Dr. McIvor said a distinction should be made between a naturally genetically manipulated animal and a transgenic animal, and that furthermore what is really being discussed in this proposal is microorganisms, rather than plants or animals. However, he said if transgenic animals were to be included in this proposal he felt that this needed to remain under RAC purview.

A long discussion ensured over the issue of transgenic animals in which Dr. McIvor continued by noting his feeling that the RAC was the proper place to review such issues. Dr. Wivel noted that this came back to the issue of product versus process, and that if the product, the transgenic animal, produced no risk to the environment that there was no reason to review the release unless such risk were possible. Furthermore, he added that the RAC did not possess the expertise in many of these areas to assess this risk. Dr. McGarrity added that the "Talbot Amendment" would still come into play and that if another agency were reviewing such experiments the RAC would not review such experiments unless they were funded by the NIH.
Dr. Schaechter said he felt these discussions were far afield from the question of why the RAC would maintain any function that is not purely recombinant DNA. He said that human gene therapy was an "exception" to this philosophy. He noted that the NIH Director had made a decision that the RAC not look at the issue of transgenic animals and that it is not a mandate of the committee.

Dr. Atlas asked that if the committee voted to approve the proposal to remove these sections from the *NIH Guidelines* that an advisory be sent to local review boards to tell them that the RAC is not getting out the business totally and that they need to continue to review these proposals at the local level.

Dr. McGarrity said he assumed if this proposal were passed that all of the work on the appendices currently approved by the RAC but not yet promulgated formally would be turned over to the USDA

and that they would no longer need be added to the *NIH Guidelines*.s Dr. Tolin said she would see that as the process and that the USDA Guidelines, when promulgated, would then fill in where Appendices L, M, N, and O now are proposed in the *NIH Guidelines*.

Dr. Miller asked if recombinant DNA release experiments would still have to go to the IBCs under such a framework. Dr. Tolin said they would unless they were exempt. Dr. Wivel said there were many such exempt categories and that the IBCs would still have the prerogative to look at an experiment and designate a containment level based on risk.

Dr. McIvor asked for clarification as to whether this change in wording would result in experiments which will release transgenic animals into the environment which are reviewed by another agency to not come to the NIH at all. Dr. Wivel said this was correct. Dr. McIvor said that he could not support such a proposal and that he felt these experiments were within the realm of recombinant DNA research and should be reviewed by the RAC.

Dr. Bourquin noted that even if the language were left in the *NIH Guidelines*, the project probably would not be reviewed by NIH, unless that project was supported by NIH funds. Dr. McIvor said that he did not believe this to be true since most of this type of research was being done at institutions which did have some NIH support and thus would fall under the purview of RAC.

Dr. Post moved that the RAC accept the proposal, as printed, with the condition that ORDA make any other housekeeping changes needed in the *NIH Guidelines* to be consistent with it. Dr. Schaechter seconded the motion.

There being no further discussion, Dr. McGarrity put the motion to a vote. The motion passed by a vote of 9 in favor, 5 opposed, and 3 abstentions.

Dr. McGarrity then asked the committee to take a short, 5 minute recess, and to reconvene to finish the agenda.

Dr. McGarrity called the committee back to order at 1:30 p.m., and asked Dr Ledley to present the next agenda item.

BACKGROUND INFORMATION ON THE REGISTRY OF GENE TRANSFER PATIENTS ENTITLED, *THE GENE TRANSFER PATIENT AND PROVIDER NETWORK (GENETRANET)***:**

Dr. Ledley said this proposal was a corollary to his proposal which he presented yesterday which he had developed as a result of his clinical training in the field of phenylketonuria (PKU). He described the normal clinical course of PKU, noting that one of the problems was the ability, once the problem was corrected, to track patients so that doctors could continue to assess their long-term outcome as well as to ensure that the patients, some of whom were treated at a very early age, knew that they had a congenital genetic disease which and that they continue to carry this genotype.

He said he felt the same type of network needed to be set up for gene transfer patients patterned after the "Register of Selected Inherited Metabolic Diseases (RSIMD)." He said this registry was used as a model because it already had been operating for a number of years and had in place the computer resources, personnel resources and other mechanical things to do it in a way that was both ethical and feasible. He said the same company that had collaborated on developing the RSIMD, Mize Information Enterprises, of Dallas, Texas, was being proposed to collaborate on this registry.

Dr. Ledley pointed to some of the things this registry could help to track. He said the following are issues dealing with the use of the viral vector:

1. Viral disease as a result of a defective vector or naturally recombinant viruses;

2. Insertional mutagenesis, leading either to malignancies, cell damage, or perhaps premature senescence of cells;

3. Contamination of vectors with other viruses;

4. Long-term immune response against either the recombinant gene products or retroviral vectors;

5. The issue of possible inheritable genetic damage;

6. Psychosocial pathology affecting either self-image, family, or social structures; and,

7. The stability and duration of functions that are put into the patient.

He noted that one good reason for having such a registry is to find adverse reactions and to make inferences about what this means relative to clinical practice, which requires large numbers of patients to be able to determine. He said this registry would be set up with the following goals:

1. To track the patient through health care providers to maintain a register of the names and addresses of the physicians of people who have had gene transfer;

2. Early and significant assessment of adverse reactions;

3. To inform the providers of procedures for surveillance, diagnosis or therapy and to allow for communication with the health care providers;

4. To point out to both the research community and the public how many procedures have been done and what are the complications that have or have not been noted; and,

5. To allow for a data base to be generated whereby both clinical investigators and others who have specific questions will be able to look for a basis for doing research in this population.

He explained that the offices of Mize Information Enterprises would essentially mail a questionnaire to health care providers on a twice-annual basis asking for information about the patients. All patients would be asked to provide informed consent. Data from either health care providers or patients will be reported back to the offices of Mize Information Enterprises who will tabulate the data. Whenever a potential adverse reaction is identified that information will be reported to Baylor

College of Medicine which will immediately evaluate the adverse reaction and inform the clinical investigators of the adverse reaction and determine whether health care providers and/or the public should be notified of this adverse reaction.

Dr. Ledley noted that this proposal will need to be funded either by theNIH or possibly private patient-oriented groups, but that it has the support of the community who have thought the most so far about gene therapy. Also, he noted that it could only be successful with the support and participation of the investigators performing human gene therapy research. He also noted that Dr. Lotze had commented that perhaps the RAC could make it a requirement of informed consent forms for this type of research to include a notation that such a registry exists and that the patients as well as the investigators should be encouraged to participate in the registry.

Dr. Leventhal said she was not opposed to the proposal, nor was she enthusiastic about it. She said there were no valid data to show that the registry would optimize patient care. She said that she was familiar with the Bone Marrow Transplant Registry and that it had not been particularly useful in determining the efficacy of bone marrow transplantation. She said the individual institutional reports of comparative studies had really been what helped to establish what is known about the efficacy and toxicity of bone marrow transplantation. She also pointed to theWilm's Tumor Registry as another similar example of a registry which failed to identify any further adverse effects of treatment than had already been reported by individual clinical investigators. She noted that funding for both these registries had been discontinued by NIH in light of the current federal budget crisis.

In summary, she said she supported the concept of a registry but not with a sense of high priority or urgency. Further, she said she did not feel the RAC should make it a requirement of approving a protocol that investigators in clinical trials participate in a registry.

Dr. Geiduschek said he and Dr. Leventhal had arrived at similar conclusions by different routes. He said the idea of setting up and running a data base to follow gene therapy patients is a good one which he thought would receive general approval and would be acceptable to the public. However, he felt the RAC should not put a stamp of "exclusive approval" on such an individual project, and that perhaps a general call for proposals for such a registry should be made and allow them to be judged on a competitive basis. He said if the committee disagreed with this view and wished to specifically approve this proposal he would make additional comments as regards to specific portions of the proposal. However, he commended Dr.Ledley for his proposal and thanked him for his work in submitting it.

Dr. Doi had some specific questions on the proposal but said he felt the proposal, if it worked in the way which was presented would provide useful information to the scientific community, the patients, and the public and that the whole concept of having the medical, scientific, and ethical answers from this data was a good one.

Ms. Buc said that the idea of a gene therapy registry seemed to be a useful one, but that she felt one thing needed was an ability for the patient to contact the registry, possibly through an freeWATS line to be able to communicate with the registry. Furthermore, she added that with such a long-range endeavor thought should be given to who would be a successor principal investigator for such an effort.

Dr. Krogstad asked if Dr. Ledley had given any thought as to whether R01 funding for this project would be the way to go since it is a long-range project and whether there might be other funding mechanisms which would be more practical. Further, he asked if Dr.Ledley had contemplated a

control group for inclusion in the registry so that valid epidemiological data could be ascertained.

Dr. Miller said his own bias was that such a registry might not be appropriate to be funded with public monies. Secondly, he said that if such a registry were developed, he wanted to know what types of gene therapy were envisioned to be included in the registry. And finally, Dr. Miller asked whether the investigators had thought about any mechanism for getting companies who are carrying out gene therapy to participate in the registry since it is likely that this may likely be the largest group of patients before too long.

Dr. McIvor asked for clarification on the term "biannually." He suggested that if the proposal was to send out a questionnaire every six months that "semi-annually" was a better term. Dr.Ledley said he would note this and ensure it was changed.

Dr. Ledley then went on to respond to the comments of the reviewers. He said that the concept of a gene registry is one which had been discussed in the past and in fact the investigators had been prodded by people at the national level to begin to look at a mechanism for setting this up. Secondly, he said that Ms. Buc's comments about communication with the patients was a key point and he said that a WATS line was envisioned to be set up as part of the registry so that the patients can call to ask questions. He said they were nervous about this in the sense that they are not the patient's treating physician and that all they will be able to tell the patient in many cases is to contact their treating physician. Also, he noted the problem of dealing with patients who move from pediatric care to adult care is a problem in the cancer registries and that patients are lost to follow-up in this process.

Dr. Ledley explained the process of measuring an adverse reaction and discussed patterns of adverse reactions as well as long-term focus on certain groups of patients. He said he was aware of the problems surrounding funding. He said he felt that if the registry is established the companies involved in gene therapy research would pay for the registry. He stressed that he felt it was important that the concept gain the backing of the RAC and that a positive response by the RAC would impact on the possibility of acquiring funding.

Dr. Anderson said that for the foreseeable future every physician who treats a patient with gene transfer/gene therapy is going to come before the RAC and that if the RAC is going to continue lifetime follow-up for patients he felt it inconsistent that it would feel uncomfortable in supporting such a registry.

Dr. Leventhal said there was no requirement for lifetime follow-up, but merely that all the data go be maintained in one place. Further, she said no one had said it should be disapproved, it was just that the level of enthusiasm was not great.

Dr. Anderson said what was being sought was support for the concept of a registry. As far as who is going to perform the work of starting up and maintaining a registry, he said that it would be difficult to send out bids and expect to get someone who would do this. He said an R01 was out of the question in light of current budget restraints. He noted that as far as funding was concerned NICHD might be open to putting some money into this, as well as other organizations, and that it's very possible, as Dr. Ledley said, that some of the biotech firms involved in gene therapy would be open to contributing to maintain such a registry.

Dr. Walters pointed out that the reason the HGTS had not discussed this proposal in detail was that it had come in after the agenda had been published for its last meeting and was unable to be placed

on the agenda at that late date.

Dr. McIvor said that since he was involved in gene therapy research and that he felt the data generated by such an endeavor may prove valuable in the long-run, that he would make a motion. Dr. McIvor moved that the RAC recognize the potential usefulness of an established registry of patients, clinicians and scientists involved in human gene transfer trials, without any reference to specific proposals. Ms. Buc seconded the motion.

There being no further discussion, Dr. McGarrity called for a vote on the motion. The motion passed unanimously by a vote of 17 in favor, none opposed, and no abstentions.

XIV. FUTURE MEETING DATES OF THE RECOMBINANT DNA ADVISORY COMMITTEE AND THE HUMAN GENE THERAPY SUBCOMMITTEE:

Dr. McGarrity called the committee's attention to the future meetings of the RAC and the HGTS. He noted the next meeting of the RAC would be on October 7, 1991, and that the Human Gene Therapy Subcommittee would be meeting on July 29, 1991.

XV. ADJOURNMENT:

Having concluded the agenda and there being no further business to be discussed, Dr. McGarrity adjourned the Committee at 2:30 p.m., on May 31, 1991.

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: 11/13/91

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