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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RECOMBINANT DNA ADVISORY COMMITTEE
SUBWORKING GROUP ON HUMAN GENE THERAPY

MINUTES OF MEETING¹

September 20, 1985

The Subworking Group on Human Gene Therapy of the Recombinant DNA Advisory Committee was convened at 9:00 a.m. on September 20, 1985, at the National Institutes of Health, Building 31C, Conference Room 9, 9000 Rockville Pike, Bethesda, Maryland 20892. The meeting was open to the public. Dr. LeRoy Walters was the Chair. The following people were present for all or part of the meeting:

Subworking Group Members:

W. French Anderson	Robert Murray
Judith Areen	LeRoy Walters
James Childress	Anne Witherby
Susan Gottesman	William Gartland, Jr.
Robert Mitchell	(Executive Secretary)

A working group roster is attached (Attachment I).

Other National Institutes of Health Staff:

Elizabeth Milewski, NIAID

¹The subworking group is advisory to the RAC, and its recommendations should not be considered as final or accepted.

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Dr. Walters called the meeting of a Subworking Group on Human Gene Therapy to order at 9:10 a.m. on September 20, 1985. Dr. Walters said the subworking group would be dealing with three agenda items: (1) a review of the comments received on the August 19, 1985, Federal Register version of the "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy (Attachment II);" (2) a discussion of the optimal presentation of the "Points to Consider" to the Recombinant DNA Advisory Committee (RAC) at the September 23, 1985, meeting; and (3) a discussion of date(s) and agenda(s) for future meetings of the Working Group on Human Gene Therapy.

Dr. Walters called the attention of the subworking group to a letter (Attachment III) from Senator Albert Gore to the Secretary of Health and Human Services (HHS) Margaret Heckler. Senator Gore said he was "writing to express his concern over the current effort of the Food and Drug Administration and the proposed Biotechnology Science Board to usurp the role of the National Institutes of Health Recombinant DNA Advisory Committee in overseeing human gene therapy experiments." He wrote he was opposed to this effort and called upon Secretary Heckler to end it immediately. Senator Gore wrote that the Recombinant DNA Advisory Committee (RAC) has adequately addressed the scientific issues to date, and it appears capable of continuing to do so for the immediate future.

Review of Comments on August 1985 Version of Points to Consider

Dr. Walters pointed out to the subworking group the differences between the August 19, 1985, version of the points to consider document (Attachment II) and the May 3, 1985, version: (1) Language indicating the applicability of the points to consider has been added to the document. (2) The first footnote has been amended to indicate the document refers to recombinant DNA and DNA derived from recombinant DNA. (3) A paragraph was deleted from the Introduction; that paragraph indicated the document is designed to cover the initial human somatic cell gene therapy protocols and that initial protocols are expected to involve only one or a few patients at a time. (4) A footnote describing the role of the Food and Drug Administration (FDA) was added to the document. (5) In the tenth paragraph of the Introduction the word "possible" had been substituted for the word "primary" in referring to consequences of somatic cell therapy. (6) A sentence indicating it is likely that possible undesirable side effects can be prevented was deleted from the document. (7) A sentence requesting that the consent form routinely be included as part of the submission has been deleted from this version of the points to consider document at the request of the National Institutes of Health (NIH) legal counsel since NIH does not routinely request consent forms. A sentence indicating the working group may request submission of the consent form in certain cases has been added to Section III-A.

Mr. Mitchell asked how the language describing FDA's role had been developed. Dr. Gartland replied that FDA legal counsel had developed that language.

Mr. Mitchell said questions had been raised at the May 3, 1985, RAC meeting concerning adequately distinguishing between the consent form and the consent

process. He said the subworking group might consider whether the points to consider document adequately makes this distinction.

Dr. Murray said currently investigators must describe to the Institutional Review Board (IRB) the method of selecting the subject(s). Investigators must also provide information on how the patient will be informed of the procedure. The IRB submits assurances to DHHS on this process. The IRB determines whether the information and process are appropriate but does not have a mechanism to monitor the consent process.

Mr. Mitchell said a whole body of law is developing for situations in which an individual surrenders fundamental rights. This body of law attempts to ensure that the individual fully understands and can make a knowledgeable decision concerning these rights. He offered as examples individuals entering a guilty plea or placing a child in adoption procedures. A similar body of law may be developing for informed consent in clinical trials.

Dr. Walters noted that the language added to Section III-A permits the working group to request the consent form in some circumstances. He said he would have preferred the points to consider indicate the working group would review consent form(s) as part of the review process. Dr. Anderson agreed it is illogical for the points to consider to contain a whole section on informed consent but not to request the form.

Dr. Walters asked whether NIH study sections routinely receive consent forms with grant applications.

Dr. Anderson said study sections receive consent forms, but they are concerned primarily with scientific and technical issues and not with the informed consent process. Dr. Murray said submission of the consent form with the grant application ensures the grant proposal was reviewed by the IRB before submission for NIH review.

Dr. Gottesman suggested the NIH legal advisor did not wish an NIH advisory group to be responsible for reviewing consent forms since such review might involve the NIH in liability issues. Dr. Walters suggested some risk liability might, nonetheless, exist for NIH in performing the scientific risk/benefit analysis.

Mr. Mitchell said he could understand the legal advisor's concern since a body of law regarding informed consent has not yet been developed. The subworking group agreed the points to consider should not at this time contain language requiring submission of the consent form.

Dr. Gartland suggested the working group should discuss informed consent issues with individuals such as Dr. Charles McCarthy of the NIH Office for Protection from Research Risks (OPRR) and Mr. Robert Larman, the NIH Legal Counsel. Dr. Gottesman suggested a meeting of the working group with these individuals be arranged.

Dr. Walters then called the attention of the subworking group to comments on the August 1985 version of the points to consider document offered by Dr. Howard Temin, a consultant to the Working Group on Human Gene Therapy.

Dr. Walters said Dr. Temin had once again pointed out that the vectors most likely to be used in human gene therapy protocols are retroviruses. The genetic material of these viruses is RNA. Dr. Temin suggested some mention of recombinant RNA should be made in the first footnote of the points to consider document.

Mr. Mitchell said RAC at the May 3, 1985, meeting had discussed the possibility of modifying the NIH Guidelines to explicitly cover recombinant RNA. The subworking group agreed that until such action is taken the first footnote should refer only to recombinant DNA.

Dr. Walters said Dr. Temin had also suggested Section I-B-1-a-(1) should be modified to read as follows:

"Describe the gene (genomic or cDNA), the bacterial plasmid or phage vector, and the delivery vector (if any). Provide complete nucleotide sequence analysis or a detailed restriction enzyme cleavage site map of the total construct."

Dr. Gottesman said the section as written contains scientific jargon; she thought Dr. Temin's suggested language was more specific. Dr. Walters agreed Dr. Temin's suggested language was more specific but thought it used many nouns as adjectives.

Dr. Anderson suggested the subworking group accept most of Dr. Temin's suggested language but not the words "cleavage site." The language would then be more precise but not use so many nouns as adjectives. The subworking group agreed to this modification.

Dr. Walters said Dr. Temin had suggested the last sentence of Section I-B-1-b-(2) should read as follows:

"What steps are being taken (and assays used with their sensitivity) to detect and eliminate any contaminating materials (nucleic acids, proteins, etc.) or contaminating viruses or other organisms in the cells or serum used for preparation of the virus stock?"

The subworking group agreed to this suggested clarification.

Dr. Walters said Dr. Temin had suggested the word "added" be substituted for the word "inserted" in Section I-B-2-a-(2), Section I-B-2-a-(4), Section I-B-2-b, and Section I-B-4-b.

Dr. Anderson admitted the word "inserted" is ambiguous, but felt the word "added" is also ambiguous. He and Dr. Gottesman noted that "added" could also refer to DNA which is simply attached to the cells' outer membrane and not introduced into the cytoplasm or the nucleus.

Dr. Gottesman said the word "added" promises less than the word "inserted;" for this reason the word "added" might be preferable in certain sections of the document since it would apply even if the DNA had not inserted in the chromosome.

The subworking group agreed to substitute the word "added" in Section I-B-1-a-(2), in the second sentence of Section I-B-1-a-(4), in the first sentence of Section I-B-1-b, and in Section I-B-4-b. They suggested the word "present" be substituted for the word "added" in the first sentence of Section I-B-1-a-(4).

Dr. Walters said Dr. Temin had also suggested the second sentence of Section I-B-2-b should read as follows:

"In what percentage of cells does expression occur only from the added DNA?"

Dr. Gottesman thought this concept was included in the second sentence of Section I-B-2-b. She suggested this sentence could be modified to more clearly state this idea and would read as follows:

"In what percentage of cells does expression from added DNA occur?"

The subworking group agreed to Dr. Gottesman's suggested modification.

Dr. Walters said Dr. Temin had also suggested a new sentence be added to Section I-B-2-b as follows:

"In what percentage of cells does expression occur from other DNA sequences as a result of the added DNA?"

Dr. Anderson questioned how one would test whether expression from other genes occurs as a result of inserting the vector in the chromosome. He did not think it currently feasible to test for such expression.

The subworking group agreed the points to consider should not request information on whether other genes are expressed if a vector inserts in the genetic material.

Dr. Walters then called the attention of the subworking group to the letter (Attachment IV) from Mr. Edward Lee Rogers on behalf of the Foundation on Economic Trends.

Mr. Mitchell said the first comment offered by Mr. Rogers is that frequent revisions of the points to consider may be needed as experience is gained in this field. Mr. Rogers did not believe the points to consider should assume how soon or how often revisions may be necessary.

The subworking group agreed with this comment. Dr. Walters said the points to consider should convey the idea that the working group will revise the document as needed; if revision is necessary more than once a year, the document will be revised more frequently.

Dr. Gottesman said the language of paragraph (3) of the Introduction to the points to consider document could better express this intent if modified as follows:

"The document will be considered for revision as experience in evaluating proposals accumulates and as new scientific developments occur. This review will be carried out at least annually."

The subworking group agreed to this modification.

Dr. Walters said Mr. Rogers also suggested the working group begin immediately to develop the procedural structure for cooperative efforts in assessing possible long-term consequences of somatic-cell gene therapy. The subworking group said the Working Group on Human Gene Therapy is committed to cooperative efforts.

Dr. Walters said Mr. Rogers had pointed out a typographical error in Section I-B-5-a; the language referring to Section III-D should refer to Section III-E. The subworking group agreed this error should be corrected.

Dr. Walters said Mr. Rogers had also suggested the working group should review its own composition. Dr. Walters said the Working Group on Human Gene Therapy had already discussed the issue of the working group's composition and is committed to seeking the opinions of consultants who can provide the requisite scientific and social expertise.

Dr. Anderson said Mr. Rogers also suggested Section I-B-5 of the points to consider should list experts in disciplines such as bioethics as "nonmedical" personnel.

Mr. Mitchell said the working group should maintain the prerogative of determining on a case-by-case basis which expertise should be represented on the research team. The subworking group agreed and rejected this proposal.

Dr. Childress said Mr. Rogers also alludes to the issue of whether there are "right" answers to some of the points to consider. Dr. Childress asked whether the working group might at some point move towards determining what would constitute "right" answers.

Dr. Walters agreed some of the points are rhetorical. The working group in some points is simply asking "have you thought about it." At this time, the working group cannot indicate how it will respond to particular issues.

Dr. Anderson said human gene therapy is a novel treatment process; in any new endeavor it is difficult to define what will be required since it is difficult to determine what is important without experience. Dr. Walters suggested a consensus may develop spontaneously in the field as experience accumulates. Changes will be made in the document when experiences suggests modifications are appropriate.

Dr. Anderson said the thinking regarding the appropriate initial patient and the appropriate approach has recently been changing. Some clinicians now feel a subject who can be helped by other options should be chosen rather than a patient for whom gene therapy is the last hope. At this time, an infant who has two years or more to live and for whom a backup therapy exists is the preferred candidate, in his view. For the first subjects, gene therapy should be the most promising of the available therapies; this situation would show whether or not the patient has been helped by the therapy.

Dr. Anderson added that when his team actually came to the point of "walking through" a gene therapy protocol with primates, they encountered technical and logistical problems which were impossible to anticipate from experience with mice. To date, most researchers have performed gene transplants with mice; mice do not present the same types of logistical problems large animals present.

Dr. Anderson said although his group has a great deal of experience with bone marrow transplants in mice, everything that technically could go wrong went wrong when they performed the procedure on monkeys. The procedure did not work in the first four monkeys; as experience has accumulated, however, the probability of success has increased. Experience with a large animal such a dog, pig, or primate is very important.

Dr. Anderson said the "gene team" approach to gene therapy appears to be the optimal approach because of the logistical problems associated with the therapy; scientists who prepare retroviral vectors will work with experts who have experience in handling large amounts of bone marrow and clinicians experienced in bone marrow transplantation. His team at the NIH will perform gene therapy on four monkeys a month every month to maintain the necessary degree of familiarity with the procedure. Gene therapy teams need experience with large animals.

Ms. Witherby asked whether the working group document should mention this obvious fact. Dr. Anderson did not think the document needed to mention this fact.

Dr. Murray suggested the subworking group reiterate the statement that the document will be refined as experience is gained.

Dr. Gottesman said Mr. Roger's final comment is that the working group should develop criteria in Part II (Special Issues) rather than simply ask questions. The subworking group agreed it is preferable at this time to simply ask investigators to think about these issues.

Dr. Childress said a tension exists in the document between the patient's right to privacy and the public's right to know. He said the working group would give primacy to the privacy of the patient and the family; the working group does not care if the public is interested in the identity of the child.

Dr. Areen suggested the portion of the points to consider referring to the right of the public to know should be cross referenced to the section dealing with privacy and confidentiality issues.

The subworking group agreed Section II-A should read as follows:

"What steps will be taken, consistent with point I-E above, to ensure that accurate information is made available to the public with respect to such public concerns as may arise from the proposed study?"

Dr. Walters asked whether it would be appropriate for the subworking group to respond to Mr. Rogers' letter. The subworking group agreed a letter to Mr. Rogers would be appropriate.

Mr. Mitchell and Dr. Childress suggested a letter of commendation and thanks might be sent to Dr. Temin for his invaluable assistance as a consultant.

Dr. Walters reported that Dr. Gartland had solicited the opinion (Attachment V) of Dr. Myron Max Levine of the University of Maryland, a former RAC member and a specialist in vaccine development. Dr. Levine had written that the points to consider are excellent, balanced, conservative, and sensitive to social issues. Dr. Levine felt a willingness to cooperate in long-term follow-up and to permit an autopsy should be prerequisites for participation in the earliest clinical trials. The subworking group agreed these procedures should be required of the initial patients.

Dr. Gartland said the NIH legal counsel would prefer Section I-D-5 not be included as part of Section I-D since Section I-D-1 through Section I-D-4 are questions while Section I-D-5 contains a statement.

Dr. Childress said Section I-D inquires how the privacy of the patient will be protected; Section I-D-5 which deals with autopsy. Follow-up could be placed in other sections of the document as well as in Section I-D.

Dr. Walters thought Section I-D-5 dealt with points which the working group considers to be particularly important in human gene therapy and which should be emphasized in informed consent.

Dr. Gottesman suggested Sections I-D-4 and I-D-5 should be modified to ask "how" patients will be informed. A question mark will be added to Section I-D-5-a. The subworking group agreed.

Dr. Childress suggested the second sentence of Section I-D-3 should be deleted since it is not really a part of informed consent. That sentence reads as follows:

"What special procedures, if any, will be followed to protect the privacy of patients and their families?"

The subworking group agreed to delete this sentence.

Dr. Walters then called the attention of the subworking group to the September 13, 1985, comments (Attachment VI) of Dr. Henry Miller of the FDA. In his first comment, Dr. Miller suggested the points to consider should state that closed sessions will be available for review of human gene therapy protocols. Dr. Gottesman said this comment had been considered by the Working Group on Human Gene Therapy at the April 1985 meeting; the points to consider document had been modified by the working group in response to this comment at that time. While the working group will not refuse to hold closed sessions, it did not wish to encourage closed session review; and the points to consider reflect this position.

Dr. Walters said Dr. Miller's second comment was that the points to consider ignore that the appropriateness of medical therapies is the result of complex risk/benefit judgments; Dr. Miller thought the points to consider imply that any risk of teratogenesis is unacceptable.

Dr. Gottesman said a complex risk/benefit judgment determines the appropriateness of any therapy, and this is also true of human gene therapy. In human gene therapy two potential risks exist: (1) vertical transmission of genetic material; and (2) horizontal transmission of genetic material. Both of these potential risks must be considered; the examples offered by Dr. Miller do not consider horizontal transmission.

Dr. Murray said the word "teratogenesis" is not appropriately used by Dr. Miller; Dr. Miller intends to refer to transmission of genetic information. Dr. Murray said transmission of genetic information is not necessarily teratogenic.

Dr. Anderson said clinicians recognize that inadvertent transmission of genetic information might occur in gene therapy; however, transmission would not be the goal of the therapy.

Mr. Mitchell said the working group drafted the document to allay public fears about germ line intervention but is aware 100% assurance against inadvertent transmission cannot be given.

Dr. Childress asked whether the document should state explicitly that some risk of inadvertent transmission to germ line cells would be acceptable.

Dr. Gottesman thought mention of inadvertent transmission in this context would raise a red flag. She thought clinicians and scientists implicitly recognize inadvertent transmission might occur.

Dr. Murray agreed; he said the working group document does not take a position on whether "inadvertent changes" in the patient's germ line are permissible. Dr. Murray said the treatment of children with leukemia offers a precedent. The effect of chemotherapy on these patients' offspring will not be known until these patients have children. Most clinicians conclude, however, a fair possibility exists that the germ line cells of these patients will be affected. Nonetheless, in childhood leukemia therapy, the risk of damaged offspring is balanced against the benefit of prolonging the life of the patient. The Working Group on Human Gene Therapy is asking for the data to make the same type of risk/benefit analysis. He felt the working group was on firm ground as long as it evaluated potential inadvertent effects and not intended changes in the germ line. Dr. Walters agreed.

Dr. Anderson said the initial protocols will involve use of modified bone marrow cells. Added DNA does not appear to be transferred from these cells to germ line cells, and effects on germ line cells are not likely.

Ms. Areen suggested the working group might communicate to Dr. Miller that it has taken no position on whether inadvertent modification of the germ line is good or bad.

Dr. Anderson suggested the word "the" should be deleted from the tenth paragraph of the Introduction of the points to consider. The subworking group agreed.

Dr. Walters said Dr. Miller's third comment suggested the first sentence in Section I-B-1-b would be more clear if it referred to the "composition" of the material.

Dr. Gottesman said the working group had considered this comment at an earlier meeting. The term "composition" is inappropriate in the context of human gene therapy protocols because composition refers to the chemical composition of a substance. The subworking group agreed.

Dr. Walters then said Dr. Miller's fourth comment suggested two new subsections be added. One of the new subsections would ask the investigator to "describe in detail the methods for harvesting, extraction, and purification and for the removal of any toxic chemicals introduced by these procedures." The second new subsection would contain a warning that penicillin and other beta-lactam antibiotics should not be used in the production of materials administered to patients.

Dr. Gottesman said the working group had considered these two proposed subsections at the April 1985 meeting. The terms "harvesting, extraction, and purification" do not apply to the initial human gene therapy procedures; the points to consider document contains the appropriate analogous language.

Dr. Anderson said the proposed subsection on beta-lactam antibodies is not relevant to human gene therapy procedures since the first clinical protocols will probably be based on procedures using modified bone marrow cells. These cells will be removed from the patient, modified, washed, and returned to the patient. Antibiotics which could cause an allergic reaction will not be present in the materials administered to the patient.

Dr. Gottesman said Dr. Miller's absolute statement prohibiting the use of beta-lactam antibiotics does not make sense since it does not specify when these antibiotics may not be used. This prohibition could be interpreted as applying to steps in the preparation of the retroviral vector in which an antibiotic might be necessary.

Dr. Walters said Dr. Miller's fifth suggestion was to add to Section I-B-1-b-(1) questions on the methods for assaying the potency of the product, the consistency of the product lot-by-lot, and the stability of the product under conditions of storage.

Dr. Murray said this proposed language had also been considered at the April 1985 meeting; at this time, it makes no sense to assume the initial clinical trials will involve commercial production. The initial gene therapy protocols will be administered on a patient-by-patient basis.

Dr. Anderson said Dr. Miller's proposed language applies in FDA reviews of drugs and biologics; however, the Working Group on Human Gene Therapy is not attempting to perform an FDA review.

Dr. Gartland asked whether the working group would review a proposal differently if FDA does not review the proposal. FDA statutes do not apply in all cases; for example FDA statutes do not apply to protocols which do not involve interstate commerce.

Dr. Gottesman said she viewed Dr. Miller's intimation that FDA might not review protocols as a threat the working group might be required to perform an FDA review. Dr. Gottesman said an FDA style review is not the working group's mandate or interest.

Drs. Anderson and Gottesman then explained that the words "potency," "consistency," and "stability" are appropriate language for drugs and biologicals but are not the correct terms to apply to human gene therapy. Genes do not have "potency." Rather the analogous term for a gene is "level of expression." The analogous information request for "stability" in gene therapy protocols is a request for information on the cell line which will be producing the retroviral vector. Cell lines producing retroviral vectors are stored in liquid nitrogen and are stable indefinitely under these conditions. "Expression in time" is the appropriate analogous term for "stability" of a gene. The language pertinent to genes is found in detail in the working group document.

Dr. Anderson said patients' bone marrow cells, which are critical to the procedure, will not be stored. He compared bone marrow transplants in human gene therapy to other organ transplantation. He said it makes no more sense to

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inquire about "stability" in human gene therapy than it would to ask about the lot stability of a kidney in a transplant operation.

Dr. Walters asked if a patient might receive a second course of gene therapy.

Dr. Anderson said it is conceivable a patient might require a second course of therapy. However, each course will be a de novo procedure, and lot consistency will not be relevant.

Dr. Walters said Dr. Miller's sixth comment was that the working group document should request a description of previously-reported similar human studies (including foreign studies) and their results.

Dr. Walters said Dr. Miller had previously made this comment to the Working Group on Human Gene Therapy. Dr. Milewski pointed out that the working group at the April 1985 meeting had added language to Section I-B-3 in response to this comment.

Dr. Walters said Dr. Miller's seventh suggestion is that Section I-B-2-c-(1)-(d) should be relocated to a position before Section I-B-2-c-(1) since Section I-B-2-c-(1)-(d) is relevant to gene therapy whether or not a retroviral system is used.

Dr. Anderson said Section I-B-2-c-(1)-(c) is appropriately placed in the document since Section I-B-2-c-(1)-(c) specifically refers to the inherent properties of retroviral vectors. He said the key question is whether the vector has sequences homologous with human sequences. Drs. Varmus and Temin specifically placed Section I-B-2-c-(1)-(d) in its current position in the document.

The subworking group agreed the language was appropriately placed in Section I-B-2-c-(1)-(d).

Dr. Anderson said the working group could consider adding parallel language to Section I-B-2-c-(3); this section deals with other host-vector systems. He could not envisage, however, that this addition would be useful since it would address pathogenicity. He did not think plasmid vectors would possess pathogenic qualities.

Dr. Gottesman said while retroviruses have a mechanism to express pathogenicity, there is no evidence to suggest plasmid vectors might possess pathogenicity mechanisms. It is, thus, not logical to pose a question in Section I-B-2-c-(3) referring to plasmid pathogenicity. If a potential pathogenicity mechanism cannot be envisaged for plasmid vectors, how could the vector be designed to avoid the consequences of pathogenicity? She said the current points to consider document is inclusive and adequately addresses the pertinent issues. The subworking group agreed.

Dr. Walters said Mr. Miller's eighth suggestion is that the phrase "specifically germ line cells" should be deleted from Section I-B-2-c-(2) because apprehension

about effects on gametes should be not greater than apprehension for effects on other critical tissues.

Dr. Walters said to ignore this issue is to ignore a source of public apprehension. Ms. Areen said Dr. Miller had offered this comment to the working group in April 1985; the working group had substituted the word "particularly" for the word "specifically" in Section I-B-2-c-(2).

Dr. Anderson said Dr. Miller was expressing a private opinion in this comment. Dr. Anderson thought germ line effects are legitimate public concerns. The subworking group agreed.

Dr. Walters then called the attention of the subworking group to Dr. Miller's ninth comment. Dr. Miller had suggested the first sentence in Section I-B-2-c-(1)-(e) would be more clear if revised to read: "Describe animal experiments completed or in progress employing protocols similar to that proposed."

Dr. Anderson said the working group had also previously considered this comment and had elected not to modify the language of the points to consider document. The working group specifically wished to request data gathered from primate testing. Dr. Anderson said the experience of his research team emphasizes the importance of testing gene therapy protocols in large animals such as primates. Dr. Anderson asked whether Section I-B-2 should include a statement on testing in "a large animal."

Dr. Gottesman said a statement on animal testing is included in Section I-B-2. She suggested the word "laboratory" be deleted from this section since the phrase "laboratory animal" to most people suggests mice or rats. Deleting this word might meet part of Dr. Anderson's concern. The subworking group agreed with this proposal.

Dr. Gottesman noted that Dr. Miller had suggested the term "in progress" be added to the language of Section I-B-2-c-(1)-(e). She questioned whether Dr. Miller's proposed language would suggest review would be deferred to await the results of "in progress" experiments.

Ms. Areen suggested the language of the section was correct as currently written. The subworking group agreed the language as written was appropriate.

Dr. Walters said Dr. Miller's tenth comment was that "selection of subjects" should be included in Section I-B-3 rather than be a separate Section I-C.

Mr. Mitchell said the working group disagreed with Dr. Miller on the emphasis which should be given this topic.

Dr. Walters said the working group also wished to include ideas of fairness and equity and for this reason made "selection of subjects" a separate section.

Dr. Childress said the working group had rejected this comment at an earlier meeting, and the subworking group should reject it this time as well.

Dr. Walters then called the attention of the subworking group to Dr. Miller's eleventh comment. Dr. Miller had suggested the first sentence of Section I-B-3 is sufficient; the other sentences require extremely complex speculation of the investigator and should be deleted.

Mr. Mitchell said Section I-B-3 is not requesting speculation since in many cases the answer will be based on experience.

Dr. Murray said the second question in Section I-B-3 does not require speculation. In some cases, a great deal of clinical literature exists; this literature could suggest potential effects.

Dr. Anderson said a complex risk/benefit analysis is exactly what a clinician performs when treating patients. This is not speculation. The subworking group rejected Dr. Miller's eleventh comment.

Dr. Walters then called the attention of the subworking group to Dr. Miller's twelfth comment. Dr. Miller had stated that in Section I-D, the initial paragraph under informed consent would provide sufficient guidance if points 1 through 5 were deleted and the following language were added to the paragraph:

"The consent form must adhere to the requirements of 45 CFR 46 and 21 CFR 50. Special attention must be paid to the applicability of the additional elements of informed consent listed in these regulations. (Include a copy of the patient consent form as part of the documentation requested in Part III, below.)"

The subworking group agreed the working group had discussed this suggestion at the April 1985 meeting and had determined it wished to highlight specific points. The subworking group agreed no change was indicated at this time.

Dr. Walters said Dr. Miller's thirteenth comment was that in Section I-E the initial paragraph under "Privacy and Confidentiality" would provide sufficient information without points 1 and 2; points 1 and 2 should be deleted.

Ms. Areen felt the working group document highlighted certain important issues. She felt this section of the document should not be altered.

Dr. Anderson agreed the working group wished to consider these issues. He said the working group document is not meant to be an FDA review. The subworking group rejected Dr. Miller's thirteenth comment.

Dr. Walters said Dr. Miller in his fourteenth comment said Section II-B is irrelevant to judging the appropriateness of a clinical trial.

Dr. Walters said the working group had included this section in the document in the hope of encouraging companies to take the patent route in protecting confidential information. This would permit greater public participation in review of human gene therapy proposals.

Mr. Mitchell said the key issue is whether the RAC and the working group would encourage public review of proposals.

The subworking group rejected Dr. Miller's fourteenth comment.

Dr. Walters said Dr. Miller in his fifteenth point expressed concern that the interrogatory style of the document may be interpreted as strident or even adversarial.

Dr. Gottesman did not think the document was perceived as strident or adversarial.

Dr. Anderson said there is no more adversarial organization than the FDA; he also found it extraordinary that Dr. Miller would attempt to give advice on how not to be adversarial.

[Executive Secretary's Note: The modified version of the points to consider is appended to these minutes as Attachment VII.]

Presentation to the RAC at the September 25, 1985, Meeting

Dr. Walters then asked the subworking group to suggest the optimal manner to present this document to RAC at the September 23, 1985, meeting. He said he would prefer that RAC formally accept this document and come to closure.

Dr. Gottesman suggested it might be useful to send to RAC a list of the modifications the subworking group introduced into the document at the September 20, 1985, meeting; this list would show none of the subworking group's modifications were substantive.

Dr. Anderson said the working group had received four comments on this version of the document: one set of comments was received from the working group's ad hoc advisor, Dr. Temin; the second set of comments was from Dr. Miller of the FDA; the third set of comments was from Mr. Lee Rogers on behalf of the Foundation on Economic Trends; and the fourth set of comments had been solicited from Dr. Myron Max Levine by Dr. Walters. The working group received only one set of comments from the general public--those of Mr. Rogers. In general, Mr. Rogers' comments were supportive.

Mr. Mitchell suggested Dr. Walters present to RAC a short history of the development of this document; this short history would then be part of the public record.

Dr. Gottesman asked Dr. Walters to remind RAC that the points to consider are a working document which will not be incorporated into the NIH Guidelines.

Mr. Mitchell asked Dr. Gartland how the document would be disseminated if accepted and adopted by RAC.

Dr. Gartland said the document would be published in the Recombinant DNA Technical Bulletin and sent to IRBs and IBCs.

Future Meeting Dates and Agendas

Dr. Walters asked the subworking group for suggestions on an appropriate date and appropriate agenda items for the next meeting of the Working Group on Human Gene Therapy. He suggested the working group in future meetings might: (1) continue a process of "self-education;" (2) discuss informed consent issues with representatives of OPRR and the NIH legal advisor; and (3) discuss germ line modification.

Dr. Gartland suggested the working group not focus specifically on germ line modification but discuss this issue in the context of other scientific issues.

Dr. Gottesman suggested the working group might consider meeting on the day following the winter/spring RAC meeting. RAC members who wish to attend could attend the working group meeting. Alternatively, some portion of the working group discussion could be scheduled as part of the RAC agenda. Certain topics, however, such as informed consent might be better discussed at a working group meeting.

Dr. Walters supported the suggestion to combine the working group and the RAC meetings; this would accentuate the ties between the RAC and the Working Group on Human Gene Therapy.

Dr. Anderson suggested another issue which should be discussed by the working group; i.e., when would it be appropriate for investigators to submit protocols to the working group for review. Some protocols may be sent to several different committees before being submitted for RAC review. He asked if investigators might send protocols to the working group before official submission for RAC review. He said important time would be lost if investigators must wait for IRBs and IBCs to complete review before the working group can begin review.

Dr. Gottesman thought the points to consider preclude RAC from reviewing the proposal before IPC and IRB review is complete. The points do not, however, preclude the working group from considering proposals before IRB and IBC review is complete. The working group would not, however, offer any recommendation before IRB and IBC approval is received.

Ms. Areen suggested the Introduction of the document might be modified to state:

"Investigators are invited at their discretion to submit their proposal to the working group for simultaneous review during IRB and IBC review."

The subworking group agreed the language might read:

"The principal investigator is invited to submit a copy of the protocol to the RAC and its working group at the time of submission to the IRB and the IBC."

Ms. Areen said protocols should not be treated as public documents until IRB and IBC review is completed. Dr. Murray agreed the IRB review process could be prejudiced by the release of information before completion of review.

Dr. Gartland said it would be very difficult under the present system to maintain confidentiality after submission of a proposal to the working group and RAC.

Dr. Walters suggested it was not appropriate to include any language on this topic in the points to consider without greater consideration of the ramifications. Dr. Gottesman agreed and pointed out that the points to consider as written do not forbid the working group from considering proposals before approval by IBCs and IRBs.

The subworking group agreed this issue should be considered in greater detail by the working group.

The meeting was adjourned at 12:45 p.m.

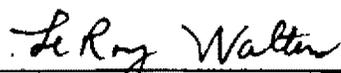
Respectfully submitted,


 Elizabeth A. Milewski, Ph.D.
 Rapporteur


 William J. Gartland, Jr., Ph.D.
 Executive Secretary

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

12/11/85
 Date.


 LeRoy Walters, Ph.D.
 Chair

Becky Lawson

RECOMBINANT DNA ADVISORY COMMITTEE

NATIONAL INSTITUTES OF HEALTH
BUILDING 31, CONFERENCE ROOM 10
BETHESDA, MARYLAND

JANUARY 27, 1986

MAILING II



National Institutes of Health
Bethesda, Maryland 20205
Building : 31
Room : 3B10
(301) 496- 6051

January 10, 1986

MEMORANDUM

To: Members
Recombinant DNA Advisory Committee

From: Executive Secretary

Subject: January 27, 1986, Meeting - Mailing II

An agenda and an updated list of primary reviewers are included in this mailing.

Enclosed for your consideration at the January 27, 1986, meeting are the following additional items:

- Draft Minutes of September 23, 1985, meeting.....1256
- Establishment of Biomedical Ethics Board.....1257

Please bring all these materials with you to the meeting.


William J. Gartland, Jr., Ph.D.

Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RECOMBINANT DNA ADVISORY COMMITTEE

BUILDING 31C, CONFERENCE ROOM 10
BETHESDA, MARYLAND

JANUARY 27, 1986

AGENDA*

- I. CALL TO ORDER.....9:00 a.m.
- II. MINUTES OF SEPTEMBER 23, 1985,
MEETING.....#1256.....Dr. McGonigle.....9:05 a.m.
Ms. Witherby
- III. PROPOSAL TO MODIFY APPENDIX J.....#1250/IV...Dr. Saginor.....9:15 a.m.
1253 Dr. McGonigle
Dr. Mills
- IV. PROPOSAL TO MODIFY APPENDIX C.....#1250/II...Dr. Friedman.....9:30 a.m.
1254 Dr. Cohen
Dr. Clowes
Dr. Davis
- V. PROPOSED REVISION OF APPENDIX C-I.....#1250/III..Dr. Friedman.....10:30 a.m.
1251 Dr. Gottesman
Dr. Joklik
Dr. Rapp
- VI. PROPOSED MODIFICATIONS OF THE.....#1250/I....Dr. Gottesman.....11:00 a.m.
GUIDELINES TO REFER TO RECOMBINANT 1252 Dr. Friedman
RNA Dr. Rapp
Dr. Clowes
- VII. REPORT OF THE WORKING GROUP ON VIRUSES.....Dr. Gottesman.....11:30 a.m.
NOVEMBER 12, 1985 Dr. Friedman
Dr. Joklik
Dr. Rapp
- LUNCH.....12:30 p.m.
- VIII. REPORT FROM HUMAN GENE THERAPY.....Dr. Walters.....1:30 p.m.
WORKING GROUP

*All times on this agenda are estimates. The actual time for consideration of an item may be earlier or later than indicated.

- IX. SCIENTIFIC SESSION ON HUMAN GENE THERAPY
- A. PROPECTS FOR HUMAN GENE THERAPY.....Dr. Martin.....1:45 p.m.
- B. GENE TRANSFER USING RETROVIRUSES.....Dr. Miller.....2:45 p.m.
- C. ROLE OF ALLOGENEIC BONE MARROW.....Dr. Parkman.....3:45 p.m.
TRANSPLANTATION IN CORRECTION OF
GENETIC DISEASES
- X. DATES OF NEXT MEETINGS--May 12, 1986.....4:45 p.m.
September 29, 1986
- XI. ADJOURNMENT.....5:00 p.m.

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PRIMARY REVIEWERS

Dr. Clowes.....1250/I, 1250/II, 1252, 1254
Dr. Cohen.....1250/II, 1254
Dr. Davis.....1250/II, 1254
Dr. Friedman.....1250/I, 1250/II, 1250/III, 1251, 1252, 1254
Dr. Gottesman.....1250/I, 1250/III, 1251, 1252
Dr. Joklik.....1250/III, 1251
Dr. McGonigle.....1250/IV, 1253, 1256
Dr. Mills.....1250/IV, 1253
Dr. Rapp.....1250/I, 1250/III, 1251, 1252
Dr. Saginor.....1250/IV, 1253
Ms. Witherby.....1256