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

RECOMBINANT DNA ADVISORY COMMITTEE
WORKING GROUP ON SOCIAL AND ETHICAL ISSUES
MINUTES OF MEETING¹

DECEMBER 13, 1983

The Working Group on Social and Ethical Issues was convened at 10:15 a.m. on December 13, 1983, in Building 31, Room 7A24, at the National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20205. The meeting was open to the public. Mr. Robert Mitchell was Chair. The following were present for all or part of the meeting:

Working Group Members:

Susan Gottesman	Robert Mitchell
Jean Harris	Elena Nightingale
John Harvin	LeRoy Walters
John Littlefield	Elizabeth Milewski
Gerard McGarrity	(Executive Secretary)

A Working Group roster is attached (Attachment I).

Government Liaison Representative:

Henry Miller, Food and Drug Administration

Other National Institutes of Health Staff:

Rosalind Gray, OD
John Fletcher, Clinical Center
Joan Porter, OD

Other:

Kim McDonald, Chronicle of Higher Education

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

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Mr. Mitchell, the Chair, called the meeting of the Working Group on Social and Ethical Issues (formerly the Working Group for Development of Response to President's Commission's Report on Ethical and Social Issues) to order at 10:15 a.m., December 13, 1983. He began by summarizing the history of RAC's recommendation to consider ethical, legal, and social implications of genetic engineering in humans.

At its April 11, 1983, meeting, the Recombinant DNA Advisory Committee (RAC) endorsed a proposal to form a working group to comment and report to RAC on the "Report on the Social and Ethical Issues of Genetic Engineering with Human Beings" issued in November 1982 by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.

The President's Commission report entitled "Splicing Life" suggested continuing oversight of the field of genetic engineering is desirable and outlined three possible oversight mechanisms.

1. Build on the successful history of the RAC. The composition of RAC could be modified to that of a public-private sector body such as those that have operated in other areas. The Federal Interagency Committee on Recombinant DNA could be reactivated.
2. Create a Genetic Engineering Commission of 11 to 15 members from outside the government which could meet regularly to deal solely with this field. This group could have a majority of nonscientists and draw on a series of technical panels to provide expertise in laboratory research, agriculture, manufacturing, medicine, government, and international issues.
3. Activate a President's Commission to oversee important developments in the biomedical arena. Oversight of genetic engineering could be integrated into the consideration given other biomedical areas. In this case, however, limited attention would be given to issues such as agriculture and patenting questions.

In response to the RAC directive to evaluate the options presented in "Splicing Life," the Working Group for Development of Response to President's Commission's Report on Ethical and Social Issues met on June 24, 1983, at the NIH. The working group agreed, unanimously, to forward the following recommendation to RAC to be considered at the September 19, 1983, RAC meeting.

"The Working Group agrees that there is a need for ongoing consideration of the ethical and social implications of the application of genetic technology to humans. Within this context, RAC should be prepared to consider social and ethical issues related to the applications of recombinant DNA technologies. For specific cases which come before the committee, RAC should consider explicitly issues such as those raised in the "Splicing Life" report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.

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"We, therefore, recommend that:

- "1. The membership of the RAC be modified to include adequate representation to deal credibly with these issues.
- "2. Procedures should be developed for the coordinate consideration of experiments involving the use of recombinant DNA technology in humans by Institutional Review Boards (IRBs), the Office of Protection from Research Risks (OPRR), the Food and Drug Administration (FDA), Institutional Biosafety Committees (IBCs), the Office of Recombinant DNA Activities (ORDA), and the Recombinant DNA Advisory Committee (RAC).
- "3. The NIH Guidelines for Research Involving Recombinant DNA Molecules should be reviewed for their adequacy and clarity in dealing with human experimentation.

"We recognize that the issues which will be dealt with by the RAC represent only some of the social and ethical issues associated with the applications of genetic and biomedical technologies. In addition, we believe that the general oversight function needed for these broader issues is not easily combined with the RAC's role in setting Guidelines and reviewing specific experiments. The expertise and experience of the RAC will be available to bodies which may exercise oversight of the broader issues. We expect continuing national discussion to lend new insight in dealing with the specific cases to be considered by RAC."

The RAC discussed this proposal at its September 19, 1983, meeting. It was noted that the recommendation was based on several premises. These are: (1) there is currently no other national body that deals with ethical issues in the biomedical field; (2) RAC's expertise could be supplemented by adding experts in the ethical issues of using human subjects; and (3) RAC would review proposals on a case-by-case basis in response to investigator-initiated research. RAC's review would supplement review by Institutional Biosafety Committees (IBCs) and Institutional Review Boards (IRBs). The RAC unanimously accepted the working group's recommendation.

Mr. Mitchell said RAC requested the Working Group on Social and Ethical Issues at its December 13, 1983, to discuss questions such as whether the language of the Guidelines as currently written is adequate, or how review procedures would function.

Rosalind Gray of the Division of Legislative Analysis at the NIH said the House of Representatives in its closing hours before recess had passed major legislation concerning the NIH. That bill is an amalgamation of earlier versions of bills concerning the NIH. This compromise legislation contains an amendment to create a "President's Commission on the Human Application of Genetic Engineering." The proposal, originally sponsored by Albert Gore, Jr. (D-Tenn), would establish a 15 member panel to monitor developments in this

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area and consider related ethical issues. The commission would be given a 3-1/2 year life span. The Senate equivalent of the House NIH bill is currently bottled up in committee. It is uncertain whether the Senate can reach a compromise which would release the NIH bill. Moreover, the Senate bill does not contain language pertaining to the creation of a genetic engineering commission. Should the Senate legislation pass, the House and Senate would have to compromise to design final legislation. It is not known whether the proposal to establish a genetic engineering commission would be part of that final compromise legislation.

Dr. Nightingale pointed out that even if language establishing a commission on human genetic engineering is legislated, money would have to be appropriated for this purpose. She felt RAC might be confronted with a proposal to utilize recombinant DNA techniques in treating human genetic deficiencies before Congress acts. Under this circumstance, RAC must decide upon its course of action.

Ms. Joan Porter of the Office for Protection from Research Risks reported that the Assistant Secretary for Health forwarded a decision memorandum dealing with the issue of whether the Department of Health and Human Services (HHS) should reactivate its Ethics Advisory Board. No action has yet been taken on that issue. In addition, Ms. Porter noted that the function of the Ethics Advisory Board as defined in the regulations is broad and could encompass a number of areas including recombinant DNA issues.

Mr. Mitchell noted that although there may be at some future time other mechanisms to deal with these issues such as an Ethics Advisory Board or a President's Commission none currently exists, and no prediction as to when one might exist can be made.

Mr. Mitchell said that RAC risks being criticized if it does not evaluate these proposals from an ethical standpoint. He felt such a criticism is voiced implicitly in the report "Splicing Life."

Mr. Mitchell suggested that the Working Group on Social and Ethical Issues attempt to develop some suggestions as to how RAC might deal with these issues.

He offered the following issues for consideration by the working group.

1. Should a risk vs. benefit type of review be instituted for these proposals?
2. Should RAC constitute a working group on ethical and social issues for the purpose of reviewing these proposals?
3. Should working group review be conducted prior to RAC review, or should the working group review ethical considerations after RAC has reviewed the proposal for compliance with the NIH Guidelines for Research Involving Recombinant DNA Molecules?
4. Should the Guidelines be amended to reflect RAC's recommendation that legal, ethical, and social issues be considered in reviewing experiments involving recombinant DNA and human genetic engineering? If so, how should the Guidelines be amended?

5. Are there areas of biotechnology which RAC should review, but for which the Guidelines as written do not mandate review? Could and should the RAC mandate be expanded?
6. Can a "checklist" of issues be developed for these types of experiments?
7. What types of consequences should be the primary emphasis of the review?
8. Does RAC as it is currently constituted have sufficient credibility to perform such a review?

Mr. Mitchell felt the group reviewing social and ethical issues in biomedicine must possess sufficient technical expertise to evaluate the proposal in a scientific as well as ethical context.

Dr. Walters offered a proposal for discussion. He proposed that:

1. A working group be established with the mandate of advising RAC.
2. The working group be composed of nine members (including the chair) with equal biomedical and lay representation (e.g., specialists in bioethics and law).
3. The working group would use available human research guidelines and sources such as "Splicing Life," OPRR guidelines, etc., rather than developing specific guidelines.

Dr. Walters said the proposed working group would review and structure proposals; RAC will continue to fill its role in reviewing and recommending such proposals.

Dr. Gottesman asked if the proposed working group would perform the same functions as IRBs. Dr. Fletcher pointed out that IRBs do not discuss long range consequences of research, indeed the Code of Federal Regulations (45 CFR 46) regarding protection of human subjects explicitly states that IRB review is to focus on the individual human subject and his rights. Dr. Fletcher said a RAC working group on this issue could provide a forum for discussing long term consequences to society. The IRB should, however, first review the proposal to assure protection of the human subjects; a working group would then review the proposal for the consequences to society.

Dr. McGarrity stated his view that guidelines are necessary and should be developed by this proposed working group. Dr. Harvin disagreed. Dr. Harris thought the issues with which a working group will contend will be influenced by societal demands, perceptions, etc. Demands and perceptions may evolve. For this reason, she thought proposals will have to be evaluated on a case-by-case basis. She pointed out that RAC's mandate will be limited; and RAC cannot address all the issues in the biomedical field. A working group might be a temporary partial solution. Dr. Nightingale thought the working group should have sufficient expertise to credibly review the proposals and agreed that the working group should not be permanent.

Dr. Miller said the FDA must approve experiments involving introduction of a new substance into humans. He said FDA evaluates risk vs. benefit and reviews consent forms, clinical procedures, licensing, etc., but does not consider ethical issues. Dr. McGarrity asked Dr. Miller how FDA would review a proposal dealing with human genetic engineering. Dr. Miller said the Office of Biologics would evaluate the following information: (1) analytic testing data to verify the product's identity, purity, and potency; (2) a description of the manufacturing process; (3) protocols of clinical trials; (4) the qualifications of the principal investigators; and (5) elements of informed consent.

Mr. Mitchell asked if the proposed working group would evaluate the societal impact of field testing and release into the environment of organisms containing recombinant DNA. Drs. Nightingale and Gottesman felt a second working group with a different composition might be better suited to conduct such a review. Dr. McGarrity pointed out that the Environmental Protection Agency (EPA) may have statutory authority to regulate certain activities involving environmental release of genetically altered microorganisms.

Dr. Fletcher said some of the earliest proposals involving introduction of DNA into humans will probably be attempts to correct single gene, "classic" inborn errors of metabolism such as Lesch-Nyhan syndrome or phenylketonuria through somatic cell therapy. He felt most individuals would perceive the merit in such attempts. He warned though that the line between desirable and undesirable subjective alterations is fuzzy. He thought an example of subjective changes would be modifications made for aesthetic purposes such as increased height or the modification of character traits. He questioned whether society would ultimately be able to distinguish between desirable and undesirable subjective modifications.

Dr. Miller pointed out that aesthetic issues exist in the use of anabolic steroids, growth hormones, breast implants, rhinoplasty, etc. Dr. McGarrity replied that these considerations only apply to a single individual. Alteration of the gene pool through use of recombinant DNA techniques could apply to society as a whole.

Dr. Nightingale said the human subject guidelines are inadequate when applied to human germ line manipulations such as those involving embryos, sperm, or eggs. Can the human subject guidelines be applied to cells in vitro? Who will be protected? The cells in vitro which might become a human being? These types of questions will not be addressed by FDA or the IRBs.

Dr. Gottesman said proposals should be viewed on a case-by-case basis, yet she pointed out the problem inherent in such an approach; the first proposals coming to RAC will probably involve somatic cell therapy to correct or ameliorate single gene defects. These proposals will pose simpler ethical questions than the proposals which will follow, yet the first proposals may set precedents.

Dr. Gottesman expressed her belief that proposals involving human genetic engineering should first be reviewed by the IRBs. Proposals which have IRB approval could then concurrently be reviewed by FDA and the NIH. Dr. Gottesman

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thought either RAC or a RAC working group might effect NIH review, but she preferred the concept of prior review by a working group as a working group can be more flexible. Dr. Walters agreed with Dr. Gottesman.

Dr. Nightingale asked if the first recommendation of the Working Group for Development of Response made at the June 24, 1983, meeting was being acted upon. The recommendation reads as follows:

"The membership of the RAC be modified to include adequate representation to deal credibly with these issues."

Dr. Milewski replied that it was. She pointed out, however, that members can easily be appointed to a working group.

Dr. Mitchell asked whether meetings of the proposed working group would be open to the public. Dr. Gottesman thought these meetings should be open, but she felt the working group would be more flexible if their meetings did not have to be announced in the Federal Register. She reasoned that RAC would offer a recommendation on the proposal, and RAC meetings are open to the public and announced in the Federal Register 30 days prior to the meeting. Any principles, structures, or questions evolved by a working group could be published in the Federal Register prior to the RAC meeting.

Dr. Littlefield asked how experiments involving use of recombinant DNA technology in humans would be forwarded to RAC for review. Dr. Gottesman replied that the Guidelines should specify which proposals are to come to the NIH. She thought the IRBs or the principal investigators might forward these types of proposals to RAC. Dr. Walters asked Ms. Porter if the IRBs would review all proposals in this category. Ms. Porter replied that if an institution has an Assurance of Compliance (in accordance with 45 CFR 46) with HHS, proposals involving human subjects and recombinant DNA must be reviewed by an IRB. However, if the institution has no HHS assurance and will not be receiving HHS funds for the project, it is conceivable that an IRB would not review this type of project.

Dr. McGarrity asked Dr. Miller to describe the time scale for FDA review of proposals of this type. Dr. Miller said the FDA has 30 days to review the proposal. Unless the proposed studies are specifically interdicted by FDA the investigator can automatically proceed. Dr. Miller pointed out two concerns the working group should consider: (1) proposals frequently involve negotiations between FDA and the investigator; a working group should be prepared to perform these types of negotiations; and (2) questions of confidentiality. He noted that the FDA does not even admit to receiving an application in order to protect the proprietary interests of the submitter. Dr. Gottesman felt the NIH would not deal with questions of confidentiality as she did not feel issues relevant to confidentiality would be relevant to the working group. Mr. Mitchell agreed saying the first such proposals of this type will not be processed on a "fast track."

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Dr. Littlefield said genetic engineering experiments utilizing recombinant DNA techniques are currently being performed with animals. He asked if the Guidelines adequately cover this research. Dr. Gottesman replied that Section III-B-4-b of the Guidelines specifies that these types of experiments be reviewed by the IBCs. Dr. Littlefield asked if RAC would want to review experiments which genetically modify animals through use of recombinant DNA. Dr. Harvin thought experiments involving animals should be reviewed. Dr. Gottesman said many such experiments are currently being performed, but only a small subgroup of these experiments would present a concern. Dr. Gottesman added that the animals used in these experiments would be contained as specified by the Guidelines. Humans cannot be "contained." She felt that the proposed working group should deal only with human applications. If necessary, a second working group could be formed to deal with animal issues.

Dr. Walters asked if RAC will review gene therapy experiments which do not utilize recombinant DNA techniques. Dr. Gottesman said the Guidelines do not cover those types of experiments. She offered the example of the Martin Cline case. If Dr. Cline had used a restriction nuclease to cut the DNA from its vector, the experiment would not have fallen under the Guidelines. Dr. Walters said Guidelines which deal only with a specific type of experiment set up incentives to perform manipulations in certain ways. Dr. Gottesman pointed out that in the Cline case the IRB had not approved the experiments. Dr. Walters said he was concerned about the public's perception that some research in this area will not be reviewed. Dr. Walters asked if the Guidelines could be rewritten to require procedures such as Dr. Cline's experiments to be reviewed by RAC. Dr. Gottesman said language to specify review for these types of experiments might be developed.

Dr. Walters asked if the RAC charter could be modified to give RAC a larger purview. Mr. Mitchell thought perhaps the charter could be reviewed. Dr. Gottesman suggested that a new Section III-A-4 be added to Section III-A, "Experiments that Require RAC Review and NIH and IBC Approval Before Initiation." Proposed Section III-A-4 would specify that recombinant DNA experiments involving humans should be reviewed by IRBs, IBCs, and RAC. Dr. Walters said such language would not meet his concerns about RAC's purview. Dr. Gottesman said the more sophisticated techniques, those most likely to work, will use recombinant DNA to effect the introduction of recombinant DNA into humans; and these experiments will be reviewed by RAC.

After some discussion of definitions, the working group developed the following language for a new Section III-A-4:

"III-A-4. Deliberate transfer of recombinant DNA or DNA derived from recombinant DNA into human subjects."

Dr. Miller asked that language be added indicating that this review would not preempt FDA and IRB review. Dr. Gottesman agreed and suggested that such language might be added to Section V of the Guidelines, "Footnotes and References of Sections I-IV." A footnote might read as follows:

"The requirement for RAC review should not be considered to preempt any other required review of experiments with human subjects. IRB review of the proposal should be completed before submission to NIH."

Dr. Walters asked that a footnote also be added to Section III-B-4-b since humans might be considered animals. Dr. Gottesman suggested the following footnote:

"For recombinant DNA experiments involving human subjects, see Section III-A-4."

Dr. McGarrity moved that a resolution endorsing the reinstatement of the HHS Ethics Advisory Board be sent to RAC. Dr. Littlefield felt he could not support this motion. He thought the Working Group on Social and Ethical Issues might welcome reinstatement of the HHS Ethics Advisory Board but not demand it. Dr. Gottesman pointed out that the Ethics Advisory Board might not function as the Working Group on Social and Ethical Issues anticipates. Dr. Harvin felt that such a resolution would imply criticism of HHS; thus, he said he would not support it. Dr. Walters pointed out that a similar discussion had occurred at the June 24, 1983, meeting of the Working Group for Development of Response; at that meeting no resolution was adopted. Dr. Harvin suggested that if some statement is to be sent to RAC the following language might be more appropriate:

"We would feel the implementation of the functions of the Ethics Advisory Board would be supportive of efforts to address moral and ethical problems in medicine."

Dr. McGarrity agreed to this substitute language. This language was carried by a voice vote.

Dr. Nightingale said that although she had supported the statement, she felt the working group had not sufficiently thought through this issue. She noted that other groups such as a President's Commission or an Institute of Medicine group of the National Academy of Science might also be endorsed. She thought the Working Group on Social and Ethical Issues might explain its support for reinstatement of the Ethics Advisory Board by the fact it itself is a HHS working group.

Mr. Mitchell asked how the proposed RAC working group might be constituted. He noted that Dr. Walters had earlier suggested equal numbers of scientists and lay members be appointed to the working group. Dr. Walters suggested individuals with expertise in basic science, clinical medicine, law, and ethics might be appointed to the working group. Dr. Harvin suggested that no specific composition be designated; rather ORDA might appoint members as the need arises. Dr. Milewski indicated that in most instances the RAC chair in consultation with ORDA appoints working group members. Dr. Walters asked if a total of 9 members including the chair was a reasonable size. The working group agreed that 9 members would supply adequate expertise.

Mr. Mitchell asked if the proposed working group should develop and institute guidelines. Drs. Gottesman, Harvin, Harris, and Walters thought a case-by-case

approach was more appropriate. Dr. Littlefield suggested that the report "Splicing Life" could be used as a resource. Dr. Walters agreed noting that the recommendation made to RAC at its September 19, 1983, meeting by the Working Group for Development of Response to President's Commission's Report on Ethical and Social Issues was "to consider social and ethical issues related to the application of recombinant DNA technologies. For specific cases...RAC should consider explicitly issues such as those raised in the 'Splicing Life' report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research."

Dr. Nightingale said the report "Summing Up" by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research might also be a resource. "Summing Up" describes three ethical principles which should predominate in medicine and medical science. These are: (1) that the well-being of people be promoted; (2) that people's value preferences and choices be respected; and (3) that people be treated equitably. Dr. Nightingale requested that the portion of "Summing Up" describing these principles be attached to the minutes (Attachment II).

Dr. Walters asked how the RAC review process for these proposals would be triggered. Dr. Gottesman said proposed Section III-A-4 would require these proposals be submitted to the NIH for review following IRB approval. Dr. Gottesman asked whether the working group could request that FDA notify RAC of applications received by FDA. Dr. Walters suggested that the proposed working group have liaison members from OPRR and FDA. The Working Group on Social and Ethical Issues supported this suggestion.

Mr. Mitchell summarized the conclusions developed by the Working Group on Social and Ethical Issues. He noted that the working group had: (1) developed language to modify the Guidelines; (2) developed the concept of a working group to evaluate proposals prior to full RAC review; (3) suggested an optimal composition for such a working group; (4) offered some guidance on source materials such as "Splicing Life" and "Summing Up;" and (5) suggested mechanisms and procedures for interaction between OPRR, IRBs, FDA, and the NIH system. He then adjourned the meeting at 3:15 p.m.

Respectively submitted,

Robert E. Mitchell
Chairman

Elizabeth Milewski
Elizabeth Milewski, Ph.D.
Rapporteur and
Executive Secretary

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