

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

RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING

SEPTEMBER 19, 1983

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SEPTEMBER 19, 1983

The Recombinant DNA Advisory Committee (RAC) was convened for its twenty-eighth meeting at 9:00 a.m. on September 19, 1983, in Building 1, Wilson Hall, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20205. Mr. Robert Mitchell (Acting Chair), Attorney at Law in California, presided. In accordance with Public Law 92-463, the meeting was open to the public from 9:00 a.m. to 10:30 a.m. and from 1:50 p.m. to 3:45 p.m. The meeting was closed to the public from 10:30 a.m. to 12:45 p.m. for review of proposals involving proprietary information. The following were present for all or part of the meeting:

Committee members:

Royston Clowes	Wolfgang Joklik	Mark Mills
L. Albert Daloz	Arthur Landy	Robert Mitchell
David Friedman	Myron Levine	Mark Saginor
Susan Gottesman	Gerard McGarrity	Pieter Wensink
John Harvin	John McGonigle	William J. Gartland, Jr. (Executive Secretary)

A Committee roster is attached (Attachment I).

Ad hoc consultants:

Ann Vidaver, University of Nebraska  
LeRoy Walters, Kennedy Institute

Non-voting members:

Morris Levin, Environmental Protection Agency  
Henry Miller, Food and Drug Administration  
Marvin Rogul, Environmental Protection Agency  
Sue Tolin, Department of Agriculture  
William Walsh, Department of State

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<sup>1</sup>The RAC is advisory to the NIH, and its recommendations should not be considered as final or accepted. NIH action on many of these recommendations was published in the Federal Register on November 23, 1983 (48 FR 53056). The Office of Recombinant DNA Activities should be consulted for NIH policy on specific issues.

## I. CALL TO ORDER AND OPENING REMARKS

Mr. Robert Mitchell, Acting Chair, called the meeting to order at 9:00 a.m., on September 19, 1983. He asked whether a quorum was present and was informed by Dr. Gartland that there was a quorum. Mr. Mitchell then introduced two new RAC members: Dr. Mark Mills of Good Samaritan Hospital in Vincennes, Indiana, and Dr. Wolfgang Joklik of Duke University Medical Center in Durham, North Carolina. Mr. Mitchell then introduced the two ad hoc consultants for the September 19 meeting of the RAC: Dr. Anne Vidaver of the University of Nebraska in Lincoln, Nebraska, and Dr. LeRoy Walters of Georgetown University in Washington, D.C.

## II. MINUTES OF THE APRIL 11, 1983, MEETING

Mr. Mitchell called upon Dr. McGonigle to review the minutes (tab 1119) of the April 11, 1983, meeting. Dr. McGonigle said he believed the minutes were substantively correct and moved approval. Dr. Harvin seconded the motion. Mr. Mitchell then called for a voice vote, and the minutes were unanimously approved.

## III. PROPOSED AMENDMENT OF PROCEDURES FOR SCALE-UP OF EXEMPT ORGANISMS

Dr. McGarrity began review of the proposal (tabs 1114, 1117/II, 1121, 1124) of Dr. Irving S. Johnson of Lilly Research Laboratories, a division of Eli Lilly and Company. Dr. Johnson had proposed that procedures be modified for experiments involving more than 10 liters of culture of organisms listed in Appendix C of the Guidelines. Specifically, Dr. Johnson proposed the following two changes in the Guidelines:

- (1) Delete statements in all sections of Appendix C that refer to large-scale experiments, viz:

"Large-scale experiments [e.g., more than 10 liters of culture] require prior IBC review and approval. [See Section III-B-5.]"

- (2) Modify Section III-B-5 to read as follows:

"III-B-5. Experiments With Non-Exempt Organisms Involving More Than 10 Liters of Culture. The appropriate containment will be decided by the IBC. Where appropriate, Appendix K, Physical Containment for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules, should be used."

Dr. Johnson's letter expressed concern "over the discrepancies between laboratory scale and production scale containment requirements - particularly for organisms in the categories that are 'exempt' under laboratory conditions."

Dr. Johnson wrote that "With the large-scale containment classifications a formal part of the guidelines, it seems to us that an unnecessary constraint is placed on the IBC in its interpretation of 'appropriate' containment i.e., there are no choices other than P1-IS, P2-IS, or P3-IS."

Dr. McGarrity noted that Dr. McKinney had commented (tab 1121) on this proposal in a letter to the RAC. The comment encouraged the RAC to reject the proposal and to retain the current provisions of the Guidelines. Dr. McKinney stated in his letter:

"The Guidelines provide adequate guidance for establishing containment levels and reflect practices appropriate to these levels. ...the Guidelines provide Institutions and the NIH the necessary degree of oversight for activities involving large-scale research or production with organisms containing recombinant DNA. This oversight is viewed as essential for activities in which the NIH is a participant."

Drs. McGarrity and Wensink agreed with Dr. McKinney's observations. Dr. Wensink suggested that RAC might on a case-by-case basis recommended exempting certain E. coli strains from Section III-B-5. Dr. Gottesman said the IBC already possesses leeway in prescribing containment conditions for large-scale experiments.

Dr. McGarrity summarized a letter (tab 1124) submitted on September 14, 1983, by Mr. Max Marsh of Lilly Research Laboratories in which he offered an alternative modification of Appendix C to Dr. Johnson's proposal. Mr. Marsh's letter requested that these proposals be referred to the Large-Scale Review Working Group for evaluation. The letter suggests the particular issues in large-scale operations that might be evaluated by the working group including the use of less expensive but highly effective filters in the exhaust air system of the fermentors. Dr. McGarrity noted that Mr. Marsh's letter contained documentation, but he felt the data were sparse. Dr. McGarrity also noted that the data on the survivability of microorganisms in aerosols were generated using E. coli; E. coli is very susceptible to dehydration. These data should not be extrapolated to S. cerevisiae or to B. subtilis which are more resistant to desiccation. Mr. Marsh said the costs of P1-IS are economically significant for new facilities.

Dr. McGarrity said he did not intend to offer a motion concerning the proposals. Mr. Mitchell said the issue should be referred to the Large-Scale Review Working Group. As no motion was offered, the discussion ended.

#### IV. PROPOSAL TO INCLUDE STREPTOCOCCUS MUTANS IN SUBLIST F OF APPENDIX A

Dr. Gottesman began review of the proposal (tabs 1115, 1116, 1117/III) of Dr. Francis Macrina of the Medical College of Virginia of the Virginia

Commonwealth University. Dr. Macrina requested that Streptococcus mutans be included in Sublist F of Appendix A and be deleted from Sublist E of Appendix A of the NIH Guidelines for Research Involving Recombinant DNA Molecules where it is currently listed. Dr. Macrina argued that S. mutans should be included in Sublist F for the following reasons:

- (1) A broad host range streptococcal plasmid, pAM 1 (conferring erythromycin resistance), is conjugatively transmissible to S. mutans. Strains of S. mutans inheriting this plasmid are able to transmit it via conjugal transfer.
- (2) The report of non-plasmid associated conjugal transfer of tetracycline resistance from S. mutans to other strains of S. mutans and to S. faecalis support the claim of natural genetic transfer from S. mutans to other streptococci.
- (3) A tetracycline resistance determinant from a naturally resistant S. mutans clinical isolate shares sequence homology with the Tn916 (Tc<sup>r</sup>) conjugative transposon originating in S. faecalis.
- (4) Naturally transformable strains of S. mutans are readily transformed with plasmid or chromosomal DNA from other mutans as well as sanguis strains.

Dr. Gottesman described Appendix A. She said Appendix A is based on the idea that if two or more organisms exchange genetic information by a mechanism you expect to find in nature, no novel entities will be created by using recombinant DNA techniques to combine the DNA of these "exchanger" organisms.

Dr. Gottesman said there are a number of sublists in Appendix A; each sublist contains the organisms which have been shown to exchange genetic information by known physiological processes. Dr. Gottesman noted that S. mutans is currently included in Sublist E which permits one way transfer of Streptococcus mutans or Streptococcus lactis DNA into Streptococcus sanguis. If S. mutans were to be included in Sublist F, S. mutans could be used in two-way transfers of DNA with the organisms, S. sanguis, S. pneumoniae, S. faecalis and S. pyogenes. She said the data supported Dr. Macrina's request to add S. mutans to Sublist F of Appendix A, and she moved approval. Dr. Gottesman stated that Sublist E should also be retained as currently written since S. lactis is included in Sublist E but not Sublist F. Drs. Friedman and Clowes supported Dr. Gottesman's motion. The motion was unanimously carried by a vote of fourteen in favor, none opposed, and no abstentions.

#### V. PROPOSED MODIFICATION OF APPENDIX L

Dr. Tolin of the U.S. Department of Agriculture (USDA), a liaison representative to the RAC, introduced the proposal (tabs 1117/IV, 1120) to

modify Appendix L of the Guidelines. Dr. Tolin described the process by which this proposal was developed. The RAC Working Group on Revision of the Guidelines at its January 21, 1983, meeting recommended that guidelines for field experimentation involving plants modified by recombinant DNA techniques be developed for consideration at the April 11, 1983, RAC meeting. A proposal specifying conditions under which field testing of plants could be performed was subsequently developed by the Plant Working Group. The NIH Guidelines for Research Involving Recombinant DNA Molecules in force at that time required RAC review and NIH approval as well as IBC approval for the "deliberate release into the environment of any organism containing recombinant DNA." The proposal developed by the working group would have changed this so that provided experiments met certain criteria, growing of plants containing recombinant DNA in the field would have been able to proceed without RAC review and NIH approval. IBC approval would have been required as would notification of ORDA.

At its April 11, 1983, meeting, the RAC considered the Plant Working Group proposal and discussed it extensively. RAC made several modifications in the specified criteria and modified the procedural aspects of the proposal. The RAC recommended that the modified language be incorporated into a new appendix (Appendix L) which would require review and approval of experiments both by the Institutional Biosafety Committee (IBC) and by the Plant Working Group.

The exact language of Appendix L was subsequently developed by NIH staff based on the recommendations made at the RAC meeting. The U.S. Department of Agriculture Recombinant DNA Committee then reviewed the RAC recommendation including the proposed wording for Appendix L and endorsed adoption of this language.

The NIH accepted the proposed language and incorporated it into the Guidelines as Appendix L on June 1, 1983 (48 FR 24548 and 24580).

Dr. Tolin said that in consultation with other members of the RAC Plant Working Group, she was now proposing several amendments to Appendix L-II-C. This section specifies some of the criteria which allow the RAC Plant Working Group to review certain proposals without the requirement for full RAC review. Dr. Tolin noted that Appendix L-II-C currently reads as follows:

"Appendix L-II-C. The vector consists of DNA: (i) from exempt host-vector systems (Appendix C); (ii) from plants of the same or closely related species; (iii) from nonpathogenic prokaryotes or nonpathogenic lower eukaryotic plants; (iv) from plant pathogens only if sequences causing disease have been deleted; or (v) chimeric vectors constructed from sequences defined in (i) to (iv) above. The DNA may be introduced by any suitable method."

Dr. Tolin proposed that Appendix L-II-C be modified to read as follows:

"Appendix L-II-C. The vector consists of DNA: (i) from exempt host-vector systems (Appendix C); (ii) from plants of the same or closely related species; (iii) from nonpathogenic prokaryotes or nonpathogenic lower eukaryotic plants; (iv) from plant pathogens only if sequences resulting in production of disease symptoms have been deleted; or (v) chimeric vectors constructed from sequences defined in (i) to (iv) above. The DNA may be introduced by any suitable method. If sequences resulting in production of disease symptoms are retained for purposes of introducing the DNA into the plant, greenhouse-grown plants must be shown to be free of such sequences before such plants, derivatives, or seed from them can be used in field tests."

Dr. Tolin noted that, under the present language, the Plant Working Group might have to review proposals according to the strictest sense of the word "disease." This may preclude approval of proposals utilizing some plasmid and virus-derived nucleic acid vectors since in the strict sense their replication might be construed to be part of the disease process even if no symptoms develop in the plants. Dr. Tolin said certain of these sequences might be necessary to introduce the recombinant DNA into the plant. She said there are, moreover, methods for removing these sequences before the plants are tested in the field. The proposed modification specifies that data showing elimination of these sequences would be evaluated by the Plant Working Group.

Dr. Tolin said two transformation systems would be affected by modified Appendix L: the Ti plasmid of *Agrobacterium* and plant virus vectors such as cauliflower mosaic virus. Dr. Vidaver concurred with Dr. Tolin and said the Plant Working Group sees no danger per se in portions of the vector replicating as long as disease symptoms do not result.

Dr. McGarrity asked how sequences introduced into the plant can be subsequently removed from plants. Dr. Vidaver said selection of cells could be made in tissue culture. These cells could then be manipulated in such a way that the plants regenerated from the cells can be assayed for the presence or absence of disease causing sequences.

Dr. McGarrity moved acceptance of the proposal as it appeared in the Federal Register. Dr. Wensink seconded the motion.

By a vote of thirteen in favor, none opposed, and no abstentions, the RAC accepted the motion.

#### VI. PRESENTATION BY MR. JEREMY RIFKIN

Prior to the presentation by Mr. Jeremy Rifkin, Mr. Mitchell noted that the Department of Health and Human Services (HHS) and the National Institutes

of Health (NIH) were being sued to restrain the NIH action to permit field testing of recombinant DNA containing organisms. This action was filed by the Foundation on Economic Trends, Jeremy Rifkin, Michael W. Fox, Environmental Action, Inc., and the Environmental Task Force on September 14, 1983. On September 16, 1983, HHS was informed that the plaintiffs would seek a temporary restraining order to prevent RAC from discussing issues in closed session at this meeting. Mr. Mitchell said Judge Sirica heard the matter this morning, and the temporary restraining order was denied. He noted that the reason the session is closed is to safeguard proprietary information.

Mr. Mitchell said one of the plaintiffs, Mr. Rifkin, had requested permission to address the RAC; and in keeping with RAC policy, that request had been granted. Mr. Rifkin introduced himself as President of the Foundation on Economic Trends and read a prepared statement which is appended to these minutes as Attachment II.

Mr. Michael Fox of the Humane Society of the United States said that ecological issues are of utmost importance and urged RAC to consider the questions posed by Mr. Rifkin.

Mr. Rifkin asked if there were any ecologists on the RAC. Dr. Clowes replied that several members are bacterial ecologists. Dr. Brill said he was a RAC member from September 1979 to June 1983, and that he is an ecologist.

Mr. Mitchell enumerated the process by which the proposal of Drs. Lindow and Panopoulos of the University of California, Berkeley, was reviewed. Mr. Mitchell said this proposal was first brought before the RAC for evaluation in open session at the October 25, 1982, meeting. A summary of the proposal had been published in the Federal Register 30 days prior to the meeting for public comment. At the October 25, 1982, meeting, concerns were raised and while the RAC recommended approval by a narrow margin of seven in favor, five opposed, and two abstentions, the NIH withheld approval in a Federal Register notice dated January 10, 1983 (48 FR 1157). The NIH indicated that the investigators could bring this or a modified proposal to the NIH for consideration at a future RAC meeting and could at that time submit additional data from experiments conducted in the laboratory or greenhouse.

A revised proposal was received from Drs. Lindow and Panapolous by the NIH and summarized in the March 4, 1983, Federal Register (48 FR 9441). After the public comment period, the U.S. Department of Agriculture received one letter urging the RAC to consider the request favorably. The RAC reviewed the revised proposal at the April 11, 1983, meeting in open session; and at that time, RAC recommended approval of the revised proposal by a vote of nineteen in favor, none opposed, and no abstentions.

The USDA Recombinant DNA Committee then reviewed the proposal and recommended that it be approved.

Following the recommendations of the RAC and the USDA Recombinant DNA Committee, the NIH granted Drs. Panopoulos and Lindow permission to proceed with this field test by a notice in the Federal Register on June 1, 1983 (48 FR 24549), on the basis that it presented no significant risk to health or the environment. Language indicating this permission was added to Appendix D of the Guidelines.

Mr. Mitchell pointed out that no adverse comments were received in response to the Federal Register announcements involving this proposal.

#### VII. CLOSED SESSION

The RAC went into closed session to consider proposals from commercial concerns involving field testing of recombinant DNA containing organisms.

#### VIII. REPORT OF THE WORKING GROUP ON ETHICAL AND SOCIAL ISSUES

Mr. Mitchell, the Chair of the Working Group for Development of Response to President's Commission's Report on Ethical and Social Issues, gave a brief report to the RAC concerning the activities (tabs 1111, 1112, 1117/I, 1118) of this working group. At its April 11, 1983, meeting, the 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's report entitled "Splicing Life" suggested continuing oversight of the field of genetic engineering is desirable and outlined several possible oversight mechanisms. One approach would be to build on the successful history of the RAC. The composition of RAC could be modified to that of a public-private sector body outside the Federal government such as those that have operated in other areas. Alternatively, the Federal Interagency Advisory Committee on Recombinant DNA could be reactivated if the extent of Federal responsibility is perceived to be great.

Another format would be the creation of 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 non-scientists and may draw on a series of technical panels to provide expertise in laboratory research, agricultural and environmental uses, manufacturing concerns, human uses, and international controls.

Another approach would be to assign responsibility for oversight of genetic engineering to a body that might succeed the President's Commission. Oversight of genetic engineering could be integrated into the consideration given to social, legal, and ethical implications of other biomedical areas.

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 developed and agreed, unanimously, to forward the following recommendations to RAC to be considered at the September 19, 1983, 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.

"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 for 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.
- "(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 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."

Mr. Mitchell expressed the opinion that RAC possesses the firm grounding in the technology necessary to objectively apply ethical considerations to deliberations on proposals involving human genetic engineering. Dr. Harvin supported this view. Dr. Saginor expressed the belief that RAC should not allow fear and anxiety to dictate RAC's decisions on somatic cell therapy.

Mr. Mitchell then introduced Dr. LeRoy Walters of the Center for Bioethics, the Kennedy Institute, Georgetown University. Dr. Walters was a member of the working group.

Dr. Walters said the working group recommendations are based on several conclusions. These are: (1) there is currently no other national body comparable to the RAC that deals with ethical issues in the biomedical field; (2) RAC's expertise should be supplemented by adding experts in the area of research involving human subjects; existing Federal regulations regarding human subjects could be applied without the need to devise an entirely new code of research ethics for the area of gene therapy; (3) the appropriate role for RAC would be to 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).

Dr. Gottesman said that RAC has already implicitly included ethical considerations in its deliberations; the working group is suggesting that in the case of human experimentation the ethical considerations should be explicitly stated. She noted that the primary goal of IRBs is to protect the individual patient; there is currently no mechanism for evaluating the effect on the broader community of procedures involving use of recombinant DNA in humans.

Dr. McGarrity asked about the status of legislation to establish a presidential commission for oversight of genetic engineering in man. Dr. Gartland replied that Representative Albert Gore's (D-Tenn) bill to establish a Genetic Engineering Commission is now attached as an amendment to Representative Henry Waxman's (D-Cal) bill for the general reauthorization of the NIH. To date, this bill has not passed the House and no bill regarding such a Commission has been introduced in the Senate. Mr. Mitchell said such a Genetic Engineering Commission would probably deal with global issues rather than the specific issues of individual research projects. Dr. Walters agreed and suggested the RAC and a commission would fill complementary functions.

Dr. Gottesman moved acceptance of the working group recommendations, and agreement that RAC will review such proposals when they come before it. By a vote of thirteen in favor, none opposed, and no abstentions the motion was carried.

IX. CDC-NIH GUIDELINES AND NCI REVISION OF ONCOGENIC VIRUSES GUIDELINES

Dr. Barkley said the Centers for Disease Control/National Institutes of Health (CDC/NIH) Interagency Working Group had completed a draft of guidelines entitled "Biosafety in Microbiological and Biomedical Laboratories." He noted that the document had been distributed widely for comment, and that fewer than two dozen responses, mostly favorable, had been received. It appears that after a long and arduous process, consensus has been achieved. The working group is considering adding a section dealing with how one might use the principles contained in the document to assess the hazards of organisms not already included and a section dealing with how one judges the operational integrity of biological safety cabinets.

Dr. Barkley said the CDC/NIH document recognizes that the principal route of infection among laboratory workers is auto-inoculation and direct contact contamination, e.g., finger or hand contact with contaminated surfaces and subsequent contact with mucous membranes. Ingestion is no longer a hazard in the laboratory with the elimination of mouth pipetting. Most agents listed in the document are grouped in the level comparable to the P2 level of containment. Dr. Barkley explained that these agents were grouped together since the same techniques, essentially good laboratory practices, are used to interrupt the route of infection.

Dr. Barkley said the CDC/NIH guidelines recognize that only a few human pathogens are capable in the laboratory situation of presenting risk from direct inhalation, e.g., the agents causing Q fever and TB. The higher containment levels are reserved for this type of agent. This is not to suggest that aerosol control per se is not important in laboratory safety. Indeed, aerosol control is important not only in attempting to reduce inhalation exposure but more importantly in reducing the dissemination of materials to other laboratory surfaces which offer greater opportunity for hand to mouth or nose contact.

Dr. Barkley said the CDC/NIH document designates four levels of control: Biosafety Levels 1, 2, 3, and 4. These levels are comparable to P1, P2, P3, and P4 in the NIH Guidelines for Research Involving Recombinant DNA Molecules. Agents such as those causing Q fever and TB are grouped in Biosafety Level 3. Biosafety Level 4 is reserved for exotic pathogens for which there is currently no means of disease control such as Lassa fever.

Dr. Barkley said the philosophy on which the document "Biosafety in Microbiological and Biomedical Laboratories" is based is similar to the philosophy now being used to revise the National Cancer Institute "Safety Standards for Research Involving Oncogenic Viruses" (October 1974). Dr. Barkley said that although that review is not complete, the recommended control level for all cancer viruses including Human T-cell Leukemia-Lymphoma Virus (HTLV) will be Biosafety Level 2.

Dr. Barkley said the CDC and the NIH will at some future time formally recommend to RAC that RAC consider revising the description of the P levels in the NIH Guidelines to correspond to the Biosafety Levels set forth in the document "Biosafety in Microbiological and Biomedical Laboratories." As the Biosafety Levels are based on the P levels, Dr. Barkley said this modification would not represent a change in principle.

Mr. Mitchell asked Dr. Barkley when the final report would be available. Dr. Barkley replied that the final document "Biosafety in Microbiological and Biomedical Laboratories" should be available before the end of the calendar year.

#### X. CONTAINMENT FOR ONCOGENES AND RETROVIRUSES

Dr. Gottesman began review of a request (tabs 1113, 1122, 1123) by Dr. Stuart Newman of the New York Medical College to consider whether (1) the NIH Guidelines deal adequately with experiments involving oncogenes (those genes capable of transforming certain types of cultured cells in vitro) and retroviruses, and (2) additional risk assessment experiments in this area are indicated. Dr. Newman included two articles discussing safety issues involved in research with oncogenes. These articles are:

- (1) "Oncogenes: Implications for the Safety of Recombinant DNA Work" by Dr. Ditta Bartels which appeared in Search 14, 88-92 (1983), and
- (2) "Oncogenes, Processed Genes and the Safety of Genetic Manipulation" by Drs. Ditta Bartels, Hiroto Naora and Atuhiro Sibatani which appeared in Trends in Biochemical Sciences, 8, 78-80 (1983).

Dr. Newman contended these articles raise

"new questions about the safety of laboratory work with tumorigenic DNA. These two papers review recent progress in our understanding of the nature of oncogenes and the conditions of their expression.... Dr. Bartels and her colleagues make a strong case, in my opinion, that recombinant DNA experiments with oncogene material could present an occupational hazard."

One question deals with cloning in E. coli K-12. Dr. Gottesman reviewed the risk assessment experiments performed by Drs. Malcolm Martin and Wallace Rowe and their colleagues (Israel et al., Science, 203, 883-887 (1979) and Chen et al., Science, 203, 887-892 (1979)) to determine whether viral genomes inserted as recombinant DNA in a prokaryotic host can cause infection or tumors. In these experiments, the investigators looked at the effect of naked polyoma DNA injected into a sensitive animal, and the effects of feeding E. coli K-12 containing recombinant polyoma DNA. Tests were performed to detect the production of antibodies in mice or of tumors in hamsters. No tumors were seen when bacteria carrying the polyoma genome were injected.

Dr. Gottesman said there was a small but measurable incidence of tumors when either the naked viral DNA or purified recombinant DNA containing two copies of the viral genome were injected into hamsters. None of the mice developed a viral infection after injection with E. coli K-12 carrying the polyoma genome. Results of the experiments in which the animals were fed either naked DNA or bacteria carrying the viral genome were negative. Dr. Gottesman said Dr. Bartels questions whether these types of tests are sensitive enough to predict the outcome of exposure to oncogenes.

Dr. Gottesman said in her experience it is very difficult to design risk assessment experiments to ask and to answer the "right" questions. The question always appears to be correct when the experiments are formulated; however, by the time the experiment is completed, time has elapsed and there are new data, new information, and new questions to be addressed.

Dr. Joklik said that Dr. Bartels is arguing that cloned oncogenes and retroviruses pose occupational hazards to laboratory personnel. He said research on oncogenes is advancing very rapidly. Information published several months ago may already be out of date and occasionally may be refuted. However, current information indicates that cell transformation is a highly complex, multi-step process dependent on the interaction of numerous genes, only a few of which have been identified. Thus, it appears on present evidence very unlikely that transformation is a process that is effected by a single gene; therefore, exposure to one single oncogene probably does not pose a biological hazard. He suggested oncogenes should be, nevertheless, handled under P2 containment conditions. He said that apart from HTLV he does not know of any evidence to indicate that other retroviruses pose any hazard to humans.

Dr. Levine said Dr. Bartels' paper (tab 1113) poses two major questions: (1) can oncogenes transform cells if inadvertently inhaled, swallowed, or inoculated into a laboratory worker; and (2) can cloning in bacteria actually raise the probability that the oncogene will transform cells? He estimated that the risk associated with these events would be very low. With regard to the NIH 3T3 mouse cell assay used in these systems, he noted that 3T3 is a continuous cell line and, therefore, already different from normal cells and that some regulatory mechanism has already changed in these cells. He noted that Dr. Bartels raises the question of whether work with oncogenes constitutes an occupational hazard. However, the DNA would have to be inhaled, ingested, or inoculated. He noted that ingested DNA is unlikely to survive DNAase activity in the gut; also, the use of good laboratory technique should prevent inoculation. In summary, he concluded that Dr. Bartels has not made a case that work with oncogenes poses a real increased risk. He suggested that RAC might initiate a correspondence with Dr. Bartels to determine the types of risk assessment experiments Dr. Bartels saw as valuable. He said that the greatest deficiency in the papers is that no guidelines are put forward in terms of answering specific questions.

Dr. Clowes said that when the NIH Guidelines were originally formulated it was not known that viral oncogenes, particularly retrovirus oncogenes, in certain circumstances can be as effective as the whole virus in causing tumors. Also, viruses causing human cancer had not been discovered. The issue of what is adequate containment might be reconsidered in light of this new information.

Dr. Landy suggested that the questions raised by Dr. Bartels are answered in her own article. He quoted from Dr. Bartels' article:

"The problem pointed out is not of an epidemiological nature, as was feared at the outset of the recombinant DNA debate; instead, the focus has shifted to the realm of occupational health. The number of persons potentially affected is thus limited."

Dr. Landy stated his view that the RAC was established as the result of concerns of an epidemiological nature; i.e., that "new life forms" might spread and cause disease in the general population. He said that risk to investigators has been adequately dealt with in documents such as the CDC-NIH document "Biosafety in Microbiological and Biomedical Laboratories." Dr. Malcolm Martin attended this portion of the meeting and said Dr. Bartels argues that eukaryotic oncogenes may be potentially dangerous for laboratory workers. This is a nagging issue that has been discussed for many years. He said that he is not aware of any work that has shown that oral administration of DNA has produced a tumor or infection in animals.

Dr. Martin said that in his laboratory the cloned Harvey Sarcoma virus sarc gene, an oncogene, had been intraperitoneally inoculated into almost two dozen hamsters. The animals were observed for over 300 days and no tumors were detected.

Dr. Martin said to date no case of oncogene activation by hypomethylation has been reported. He said that it is simplistic to think that transformation in tissue culture extrapolates to some danger to animals or man.

Dr. Levine moved that Dr. Martin put this information in a letter which would be sent to Dr. Bartels. Dr. Martin agreed to do this. Dr. Joklik seconded this motion. By a vote of thirteen in favor, none opposed, and no abstentions, the motion was carried.

#### XI. SHIPMENT OF RECOMBINANT ORGANISMS - APPENDIX H

Dr. Tolin noted that Appendix H of the Guidelines describes the conditions under which organisms containing recombinant DNA are to be transported. These specifications essentially describe shipment conditions for etiologic agents and require organisms containing recombinant DNA to be packaged and labeled as etiologic agents. Questions concerning shipment conditions for plant materials have arisen with increasing frequency; should these materials

if genetically engineered be treated as etiologic agents? She said that if packages containing plant materials are labeled as etiologic agents as specified in Appendix H, the shipment will be stopped at borders by the Animal and Plant Health Inspection Service (APHIS) of USDA and denied entry.

Dr. Gartland asked if plants or plant parts could be packaged for shipment as described in Appendix H, i.e., a glass vial inside of a cardboard box inside another cardboard box. Dr. Tolin replied that plant cells in culture or very small plants might be shipped in this way. Larger plants could not be shipped in that fashion as they would not survive transport packaged in this manner.

Dr. Barkley thought the packaging requirements were appropriate for shipping microorganisms and viruses. However, he thought the Guidelines should only require recombinant DNA containing organisms which are etiologic agents themselves or contain DNA from etiologic agents to be labeled as etiologic agents.

Dr. Gottesman suggested that Appendix H be revised with respect to shipping plants containing recombinant DNA.

Dr. McGarrity suggested that if the language of Appendix is to be reconsidered or rewritten, language describing the shipping regulations for agents grown in countries where foot and mouth disease is endemic should be evaluated and perhaps included. Dr. Landy asked if such cases fall within RAC's purview. Dr. McGarrity said recombinant DNA containing viruses would be within RAC's purview.

Mr. Mitchell suggested that Dr. Tolin and an ad hoc working group examine Appendix H for potential revision.

## XII. CLOSING REMARKS AND ADJOURNMENT

Mr. Mitchell noted that RAC had held a session closed to the public earlier in the day to discuss proprietary information. He said a suggestion was made that RAC review those issues in proprietary proposals which are generic in open session and those that are proprietary in closed session. Review of these applications indicates this might be very difficult to do. He asked whether such a review procedure could be devised. Dr. Clowes said it might be possible to divide such proposals into portions for discussion in public and portions for discussion in closed session, but he did not know if such a procedure would be practical.

Dr. Wensink suggested that ORDA negotiate with the submitter to determine what might be discussed in open session. Dr. Harvin suggested that the opinion of the NIH legal advisor be sought.

Dr. Gottesman pointed out that compliance with the Guidelines by industry is voluntary. She did not think procedures should become so difficult

and complex that industry would be discouraged from seeking RAC review. Drs. Landy and Friedman agreed. Dr. Friedman pointed out, however, that industry complies with the NIH Guidelines in part because of tort law considerations. Dr. Landy said that industry in many cases does not want to reveal what it is doing.

Mr. Marsh said information contained in RAC submissions is of a very competitive nature. He said it is not so much the general concepts as most companies know in general terms what their competitors are doing, but the specifics described in the proposals which must be protected. The definition of confidentiality then has to lie with the submitter, not the reviewer. To that extent, the possibility of industries submitting proposals for public review poses a number of serious problems. Mr. Marsh felt industrial submissions could probably be divided into confidential and non-confidential material, but he thought even if this were done some dissatisfaction would still be expressed over the amount and type of material labeled confidential.

Dr. Miller said FDA and EPA have a great deal of experience in discriminating between proprietary and nonproprietary information. These agencies would be willing to help RAC discriminate between these types of information. He pointed out, however, that confidentiality issues are often subtle. For example, FDA considers the existence of an application from a given manufacturer for a given product to be a trade secret and not to be divulged until knowledge of the existence of that application becomes part of the public domain.

Mr. Daloz asked who oversees the IBCs. Dr. Gartland replied that the IBCs are registered by ORDA and that NIH has sponsored two meetings of IBC chairpeople to discuss pertinent topics. A detailed study of California IBCs has also been conducted by a group at Stanford University.

Mr. Daloz asked if procedures to delete two subcommittees from the RAC charter and institute two others had been initiated. Dr. Gartland replied that they had been initiated; a request has been sent from the Director, NIH, to the Secretary of Health and Human Services to amend the charter.

Mr. Mitchell asked the members if a RAC meeting might conveniently be scheduled for January or February 1984. Many members felt December would be more convenient. Mr. Mitchell said he would entertain a motion for adjournment. Dr. Landy moved adjournment. Dr. Mills seconded. The motion passed by voice vote.

The meeting was adjourned at 3:45 p.m.

Respectively submitted,

Elizabeth Milewski  
Elizabeth A. Milewski, Ph.D.  
Rapporteur

William J. Gartland, Jr.  
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.

3/1/84  
Date

Robert E. Mitchell  
Robert E. Mitchell  
Acting Chairman  
Recombinant DNA Advisory Committee

## RECOMBINANT DNA ADVISORY COMMITTEE

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## **FOUNDATION ON ECONOMIC TRENDS**

1346 Connecticut Avenue, NW, Suite 1010 Washington, DC 20036. (202) 466-2823

My name is Jeremy Rifkin. I am president of the Foundation on Economic Trends in Washington, D.C. I am requesting that the following issues be placed on the agenda of the Recombinant DNA Advisory Committee (RAC) meeting.

**\*Issue:** On June 22, 1983, the Subcommittee on Science, Research, and Technology and the Subcommittee on Investigations and Oversight of the Committee on Science and Technology held hearings on regulating the release of genetically modified organisms into the environment. Among those testifying were Geoffrey Karny, Senior Analyst, Biological Applications, Office of Technology Assessment (OTA); Don R. Clay, Acting Assistant Administrator of the Office of Pesticide and Toxic Substances of the Environmental Protection Agency (EPA); Martin Alexander, professor of Agronomy, Cornell University, and former chairman of the Recombinant DNA Study Group of the Environmental Protection Agency Science Advisory Board; and Frances Sharples, Zoologist, Oak Ridge National Laboratory. All of these witnesses testified that the deliberate introduction of genetically engineered organisms into the environment poses a potential danger to plant, animal, and human health. According to Dr. Alexander, "alien organisms that are inadvertently or deliberately introduced into natural environments may survive, they may grow, they may find a susceptible host or other environment, and they may do harm. I believe that the probability of all these events occurring is small, but I feel that it is likely that the consequences of this low-probability event may be enormous."

In addition, in a suit filed in Federal Court on September 14, 1983, the Foundation on Economic Trends secured affidavits from some of America's most prominent ecologists, population geneticists, entomologists, and plant pathologists corroborating the testimony of the witnesses who appeared before the June 22nd hearings in Congress. Given the wide consensus of opinion by so many distinguished experts, I would like to know why the National Institutes of Health has failed to comply with the minimum standards of the National Environmental Policy Act which requires an environmental assessment or an environmental impact statement for such experiments.

**\*Issue:** In reviewing requests for experiments that require the deliberate release into the environment of genetically engineered organisms, the RAC is responsible for assessing the risk factors that such experiments might pose to plant and animal life and to the broader ecosystem. This kind of risk assessment requires scientific expertise in the fields of ecology, botany, plant pathology, entomology, and population genetics. Yet no such scientific experts sit on the RAC. In his testimony at the June 22nd Congressional hearings, Geoffrey Karny of OTA pointed out that from a regulatory perspective, there is "an important limitation to the way the NIH guidelines deal with deliberate release....virtually all of the scientific experts on the RAC are molecular biologists or experts in human health.

No one is an ecologist..." How, then, has the RAC been able to evaluate the potential risk to plant and animal health of deliberately releasing genetically engineered organisms into the environment when it's committee has failed to include qualified scientists capable of assessing such risks?

\*Issue: In order to assess the risk factors involved in experiments designed to deliberately release genetically engineered organisms into the environment, appropriate scientific tests must exist to make the appropriate evaluations. Yet at the June 22nd Congressional hearing, Karny, Sharples, Alexander, and Clay all testified that such testing procedures do not currently exist. Their opinion has been corroborated by the distinguished scientists we have secured affidavits from in our court suit. At the Congressional hearings, Don Clay, Assistant Administrator of the Office of Pesticide and Toxic Substances, testified that "there are almost no accepted methodologies for evaluating the safety of genetically engineered products. We are still several years away from having adequate testing methods and risk analysis techniques in any of these areas" This being the case, I would like to know how the RAC could have evaluated the risk factors of each of the experiments for deliberate release when scientific experts agree that the appropriate testing procedures do not yet exist to assess the risk factors?

\*Issue: At today's RAC session, the committee will be going behind closed doors to consider granting approval for two more deliberate releases of genetically engineered organisms into the environment. This is the first time the RAC has gone behind closed doors to evaluate requests for deliberate release. The RAC contends that this unusual departure is required since the requesting parties are private corporations and need to protect trade secrets. Of course, no one is challenging the right of these companies to protect their work. However, the RAC has decided to keep the entire proceedings secret, even denying the public vital information as to the risk assessment procedures and tests that were or were not performed. The public has a right to be fully informed of such tests and to be provided a detailed environmental assessment or environmental impact statement. There is no reason why the risk evaluation portion of the proceedings can't be debated in full public session. This can be accomplished without in any way compromising the rights of the parties involved to protect the secrecy of their work.

I would like to know how the public is going to be fully informed of the risk assessment and environmental impact of these two experiments when the RAC has decided to discuss and evaluate the proposals behind closed doors.

I am formally requesting that each of the four issues I've raised be placed on the agenda for debate and discussion by the RAC.

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
RECOMBINANT DNA ADVISORY COMMITTEE  
BUILDING I, WILSON HALL  
SEPTEMBER 19, 1983  
9 A.M.

MAILING I



August 1, 1983

MEMORANDUM

To: Members  
Recombinant DNA Advisory Committee

From: Executive Secretary

Subject: September 19, 1983 Meeting - Mailing I

The next meeting of the Committee will be on September 19, 1983, at the National Institutes of Health, Building 1, Wilson Hall, 9000 Rockville Pike, Bethesda, Maryland 20205. The meeting will begin at 9 a.m. This will be a one day meeting.

Room reservations have been made for the evening of September 18 at the Bethesda Marriott Hotel ((301) 897-9400) for those of you who will need accommodations. If you wish to change or cancel these reservations, please contact Ms. Becky Connors in my office at (301) 496-6051. For late arrival (after 6 p.m.), a deposit in the amount of one night's stay (check in the amount of \$58 or American Express card authorization) is required. The hotel will not hold the room past 6 p.m. without a deposit.

Drs. Anne Vidaver and LeRoy Walters will be attending the meeting as ad hoc consultants.

A preliminary list of primary reviewers is included in this mailing.

Enclosed for your consideration are the following documents:

- Proposal of RAC Working Group for Development  
of Response to President's Commission's Report  
on Ethical and Social Issues.....1111
- Summary of reports of the President's Commission  
for the Study of Ethical Problems in Medicine and  
Biomedical and Behavioral Research.....1112

Containment for oncogenes and retroviruses.....1113

Background documents on proposed major actions.....1114, 1115, 1116

Please bring all these materials with you to the meeting.

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

Enclosures

RECOMBINANT DNA ADVISORY COMMITTEE

SEPTEMBER 19, 1983 MEETING

PRIMARY REVIEWERS

Dr. Clowes.....1113, 1115, 1116  
Dr. Friedman.....1115, 1116  
Dr. Gottesman.....1111, 1112, 1113,  
1115, 1116  
Dr. Harvin.....1111, 1112  
Dr. Joklik.....1113  
Dr. Levine.....1113  
Dr. Martin.....1111, 1112  
Dr. McGarrity.....1111, 1112, 1114  
Dr. McKinney.....1114  
Mr. Mitchell.....1111, 1112  
Dr. Saginor.....1111, 1112  
Dr. Walters.....1111, 1112  
Dr. Wensink.....1114