

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

RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING¹

SEPTEMBER 10-11, 1981

The Recombinant DNA Advisory Committee (RAC) was convened for its twenty-third meeting at 9:00 a.m. on September 10, 1981, in Conference Room 6, Building 31C, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20205. Ray Thornton (Chairman), President, Arkansas State University, presided. In accordance with Public Law 92-463, the meeting was open to the public from 9:00 a.m. to 4:05 p.m. on September 10, and from 8:30 a.m. to adjournment at 10:30 a.m. on September 11. The meeting was closed to the public from 4:05 p.m. to 5:50 p.m. on September 10 for the review of proposals involving proprietary information.

Committee members present for all or part of the meeting were:

Abdul Karim Ahmed; David Baltimore; Kenneth Berns; Winston Brill; L. Albert Daloz; Nina Fedoroff; Richard Goldstein; Jean Harris; King Holmes; Patricia King; Arthur Landy; Werner Maas; James Mason; Gerard McGarrity; Robert McKinney; Robert Mitchell; Elena Nightingale; Ramon Pinon; Mark Saginor; John Scandalios; Pieter Wensink; and William J. Gartland, Jr., Executive Secretary.

A Committee roster is attached. (Attachment I)

The following ad hoc consultants to the Committee were present:

Susan K. Gottesman, National Institutes of Health, and Norton Zinder, Rockefeller University.

The following non-voting members and liaison representatives were present:

Charlotte Bell, U.S. Department of Justice; Chia T. Chen, OSHA, U.S. Department of Labor; Timothy J. Henry, Food and Drug Administration; Herman Lewis, National Science Foundation; Henry Miller, Bureau of Drugs, FDA; Jane Shultz, Veterans

¹The RAC is advisory to the NIH, and its recommendations should not be considered as final and accepted. The Office of Recombinant DNA Activities should be consulted for NIH policy on specific issues.

Administration; Sue Tolin, U.S. Department of Agriculture; and William J. Walsh, III, U.S. Department of State.

Other National Institutes of Health staff present were:

Stanley Barban, NIAID; W. Emmett Barkley, ORS; Becky Connors, NIAID; Irving Delappe, NIAID; Richard Krause, NIAID; Elizabeth Milewski, NIAID; Stanley Nagle, NIAID; John Nutter, NIAID; Bernard Talbot, NIAID; John Venditti, NCI; Michael H. Vodkin, NIAID; and Rudolf Wanner, ORS.

Others in attendance for all or part of the meeting were:

Robert Banks, RAND Corporation; Tineke Bodde, BioScience Magazine; Irene Brandt, Eli Lilly & Co.; Meredith Broadbent; Joel M. Dalrymple, USAMRIID; Mary Ann Danello, Amer. Assoc. for the Advancement of Science and American Society for Microbiology; Mark DeOries, Genex Corporation; David Dickson, Nature; Paula Dwyer, McGraw-Hill; Mark Finkelstein, Schering-Plough Corporation; Charles Gaush, Bethesda Research Laboratories; Pat Germann, Genex Corporation; Zsolt Harsanyi, DNA Science, Inc.; Clayton Hathaway, Monsanto Company; Judith Hautala, Genex Corporation; Leslie Henderson, University of Missouri; Holly Hexter, Higher Education Daily; Philip Hilts, Washington Post; Jerry Hunter, University of Maryland; Evelyn Hurlburt, Johns Hopkins School of Medicine; Dorothy Jessup, U.S. Department of Agriculture; J. A. Johnson, Library of Congress; M. J. Johnson, Pall Corporation; Attila I. Kadar, Food and Drug Administration; Geoffrey Karny, Office of Technology Assessment; Michael Konrad, Cetus Corporation; Howard Koonse, Fort Dodge Laboratories; Paul Leibowitz, Schering-Plough Corporation; Carter Leonard, Blue Sheet; Morris A. Levin, Environmental Protection Agency; Dan Liberman, Massachusetts Institute of Technology; Max Marsh, Eli Lilly & Company; James McCullough, Library of Congress; Kim McDonald, Chronical of Higher Education; Julia Miller, Science News; Claire Nader; Nanette Newell, Office of Technology Assessment; Norine Noonan, Science and Technology Committee, House of Representatives; Ann Norberg, Monsanto Co.; Lacy Overby, Abbott Laboratories; C. J. Peters, USAMRIID; Stephen Pijar, Food and Drug Administration; William Pilacinski, Molecular Genetics, Inc.; Michael Ross, Genentech, Inc.; Michael Ryan, Schering Corporation; John Salstein, Molecular Genetics, Inc.; Jim Silverman, Stauffer Chemical; Stephanie Soucek, National Institute for Occupational Safety & Health; Laurence Storch; J. H. Stryh, President's Commission; Donna Suchmann, Hazelton Laboratories; Charles Turbyville, NIH Week; Robert Willette, DUO Research; Susan Wright, University of Michigan; and Burke Zimmerman, George Washington University.

I. CALL TO ORDER AND OPENING REMARKS

Mr. Ray Thornton, Chairman, called the meeting to order at 9:00 a.m., September 10, 1981. He welcomed five newly appointed members: Mr. Albert Daloz of Hancock, New Hampshire; Dr. Arthur Landy of Brown University; Mr. Robert Mitchell of Norwalk, California; Dr. Mark Saginor of Los Angeles, California; and Dr. Pieter Wensink of Brandeis University. Mr. Thornton noted that two other newly appointed members, Dr. David Friedman of the University of Michigan Medical School and Dr. David Martin of the University of California, San Francisco, could not attend the September 10 and 11, 1981, meeting.

Mr. Thornton, noting the resignation of Dr. Donald S. Fredrickson as Director of the National Institutes of Health, said the community would miss his counsel and leadership. Mr. Thornton said that Dr. Fredrickson had the great ability of clearly articulating the relationship between science and public policy. Mr. Thornton said that the RAC was fortunate, however, in that it would now report to Dr. Richard Krause, the Director of the National Institute of Allergy and Infectious Diseases, who has been delegated responsibility for recombinant DNA matters. In introducing Dr. Krause, Mr. Thornton said the RAC has developed great confidence in his professional and scientific judgement.

Dr. Krause extended his welcome to the newly appointed members of the committee. He called the attention of the RAC to tab 1021, in which Dr. Fredrickson had delegated to Dr. Krause responsibility for actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules.

II. MINUTES OF THE APRIL 23-24, 1981 MEETING

Dr. Mason began the review of the minutes of the April 23-24, 1981, RAC meeting by commending those responsible for the minutes. He pointed out a typographical error in Section X of those minutes. He moved approval of the minutes as written, subject to any corrections or modifications members of the Committee might wish to forward to the Executive Secretary. Dr. Scandalios concurred and seconded the motion. By a voice vote, the motion was unanimously carried.

III. PROPOSED REVISION OF THE GUIDELINES

Drs. David Baltimore and Allan Campbell, RAC members, had proposed a major revision of the Guidelines (Baltimore-Campbell proposal, Attachment II) which was considered by the RAC at its April 23-24, 1981 meeting. At the April 1981 meeting, a Working Group on Revision of the Guidelines was established to review the Baltimore-Campbell proposal as well as other approaches which might

lead to a major revision of the Guidelines. The Working Group met on June 1 and July 9, 1981. The Working Group prepared a proposal for revising the Guidelines and a summary of its actions (Attachment III). In addition, the Working Group prepared a document entitled "Evaluation of the Risks Associated with Recombinant DNA Research." Two minority reports were prepared by several members of the Working Group (Attachment IV). The Working Group report (tab 1042), the minority reports, and letters of comment (tabs 1020, 1040, 1045, 1046) were distributed to RAC members prior to the September 1981 meeting.

Mr. Thornton asked Dr. Gottesman to introduce the Working Group's report. Dr. Gottesman reviewed the highlights of the report. She noted that the revision of the Guidelines promulgated on July 1, 1981, already exempts many experiments in three major host-vector systems. The Baltimore-Campbell proposal (Attachment II) would convert mandatory Guidelines to a voluntary code of good practice and would set as containment levels those appropriate for the organism being used. The Working Group considered various approaches; the majority supported a proposal (Attachment III) which adopts the containment provisions of the Baltimore-Campbell proposal but retains the mandatory aspect of the Guidelines. The proposal has not yet been published as a proposed major action in the Federal Register. The RAC may wish to modify the proposal before its formal publication in the Federal Register for public comment.

Dr. Gottesman noted that the background document discusses basic assumptions. It is difficult to imagine hazards resulting from random combinations of DNA. Furthermore, deliberate combinations will not be harmful in most cases. However, there are still some questions about certain experiments. The issue is how to deal with the latter experiments. The proposal of the Working Group would retain IBC prereview so that there is a level of review beyond the investigator. Dr. Gottesman then reviewed the main points of the Working Group proposal. The proposed containment levels are very similar to those of the Baltimore-Campbell proposal, i.e., containment would be largely based on the pathogenicity of the host. For all non-exempt experiments, at least the P1 level would be recommended. The Working Group proposal eliminates reference to biological containment in Part III of the Guidelines. The Working Group proposal also adds an admonition which reads as follows:

"If there is clear evidence that the donor DNA will significantly change the pathogenicity of the host, the containment level appropriate to the anticipated change will be applied."

While the Baltimore-Campbell proposal would be a voluntary code of practice, the Working Group proposal retains IBC prereview of covered experiments and retains Section IV-G of the Guidelines which discusses possible penalties for failing to follow the Guidelines. However, the Working Group recommends eliminating membership requirements for IBCs currently specified in Section

IV-D of the Guidelines. While the Baltimore-Campbell proposal retains the prohibition section of the Guidelines (I-D), the Working Group proposal eliminates the prohibitions on the basis that currently prohibited experiments would be prereviewed by an IBC in their proposal. Dr. Gottesman said that she felt that the major issues for discussion are: prohibitions, prereview of covered experiments, and containment levels.

Dr. Berns noted that five Working Group members, including himself, submitted a minority report which disagrees with the Working Group's proposal to retain the mandatory nature of the Guidelines. The minority report recommends elimination of Part IV of the Guidelines.

Dr. Goldstein said that he agrees with parts of the Working Group report. He said that IBCs are still needed although a survey in California has indicated great variation in IBCs. He also said that prohibited experiments need to be more clearly considered.

Dr. Harris said that she felt that the Working Group's report is an acceptable compromise.

Ms. King said that the report suggests a direction for movement but that details need to be worked out. She said that if there are Guidelines, there should be sanctions. She said that distinguishing NIH grantees from non-grantees is not unique; she cited the situation with human experimentation. Ms. King said that she strongly favors retention of the sanctions.

Dr. Nightingale said that she supports the recommendations of the Working Group, saying that they represent a good compromise. She expressed concern about the availability of other guidelines cited in the Working Group report. In this regard, she noted the many comments received on the proposed CDC Bio-safety Guidelines for Microbiological and Biomedical Laboratories. She also expressed concern that prohibition I-D-4, dealing with deliberate release into the environment, had not been dealt with. Dr. Nightingale said there is a necessity for accountability when public funds are being used. She said the RAC needs an assessment of outside perceptions and that the background document needs further work.

Dr. Zinder then addressed the RAC. He noted that he had prepared the minority reports to the Working Group's recommendations. He said that although there is a disagreement about the administrative aspects of the Guidelines, there was unanimity in the Working Group in favor of the new proposed containment levels. He noted that although inclusion of a slightly modified Part IV was recommended by the Working Group, five members have now endorsed a minority report stating that Part IV should be removed from the Guidelines. Drs. Adelberg and Zinder also signed a second minority report recommending complete elimination of the Guidelines. Dr. Zinder said that he and the scientists concerned about recombinant DNA originally proposed guidelines which would

give guidance and not be enforced, rather than rules. He cited some of the history leading to the issuance of mandatory guidelines in 1976. Dr. Zinder said that if Part IV is retained in the revised Guidelines, there should be a strong justification for retaining it stated in a position paper. He said that he prefers that the Guidelines be rescinded and replaced with a simple recommendation. He said that if scientists are to be encouraged to speak up in the future about conjectural risks, they must be shown that when interim regulation is subsequently shown to be superfluous, it can be removed.

Dr. Baltimore said that the Baltimore-Campbell proposal was a compromise between scientific judgment that there is no justification for Guidelines being other than a code of accepted practice, and the necessity for considering political and social factors. Their proposal retained the prohibitions, which he said are one of the most noted parts of the Guidelines. It has been argued that the RAC should not consider political and social factors; however, Dr. Baltimore did not agree. He said that the prohibitions have less and less justification and that he finds no difficulty in accepting the Working Group's recommendation regarding elimination of prohibited experiments, except for elimination of the prohibition against acquisition of a drug resistance trait in those cases in which such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture. Concerned scientists originally proposed guidelines meaning only guidance and not regulations; the RAC will have to decide the future course of the Guidelines. He noted that there apparently already is general agreement in the RAC on modifying Part III dealing with containment levels and agreement on retaining the exemptions. The issue is Part IV of the Guidelines. He said that he feels that it is anomalous to retain the current procedures section of the Guidelines. However, political and social issues need to be considered. If the Federal government pulled completely out of the issue, local governments might well overreact. The Federal government needs to provide surveillance, a forum for considering questions, and an office where inquiries can be authoritatively answered. Therefore, maintenance of the RAC, ORDA, and abbreviated guidelines are necessary. Dr. Baltimore expressed support for the original Baltimore-Campbell proposal, with some modifications based on the Working Group recommendations. Dr. Zinder said that if Guidelines are to be retained, it is for political and social reasons. However the political climate has changed. In New York State, which previously passed a law regulating recombinant DNA research, a bill has been introduced to repeal the law based on the assertion that the medical institutions which perform such research in New York State have proven to be trustworthy.

Dr. Nightingale said that she agrees with most of what Dr. Baltimore said. In order to implement sound public policy there are three basic ingredients: knowledge base, commitment of leadership, and appropriate social strategy. She said that in this case there is much agreement on the knowledge base and that there is need for change and the direction of that change. There is more disagreement on the appropriate social strategy. Having Federal involvement is one method of tempering local extremism.

Ms. King noted that the Baltimore-Campbell proposal would put industry and academia on an equal footing. She said that the RAC should consider a special meeting and public hearing on the proposed changes.

Dr. Gottesman noted that the current Guidelines are flexible and that the vast majority of experiments done today are exempt. She feels that there are scientific reasons for having a group other than the principal investigator look at the experiments still covered by the Guidelines; they should be reviewed by IBCs. She said that the critical issues in Part IV of the Guidelines are IBC prereview and compliance. She said that the Working Group's proposal does not involve an immense administrative burden.

Dr. Goldstein said that he also shares concerns about the scientific issues. He noted the number of new companies becoming involved in recombinant DNA research.

Dr. Brill stated that at a recent public meeting regarding a genetic engineering company in Madison, Wisconsin, no concerns were expressed about use of recombinant DNA technology.

Dr. McKinney said that the handling of the prohibitions is an important issue. They could perhaps be changed to cautionary advisories. He also said that citation of CDC and USDA guidelines needs to be considered. He preferred that NIH retain some form of guidance over recombinant DNA research.

With regard to the proposed revision of the CDC guidelines, Dr. Berns said that he expects great improvement in the document in the near future. He had discussed proposed revisions of the NIH Guidelines at a recent Gordon conference; most scientists there did not favor complete abolition of the Guidelines and favored instead something like the Baltimore-Campbell proposal. He also cited his local Congressman's concern about the potential for increasing public concern about recombinant DNA technology. It is important in the Guidelines revision that public confidence be maintained. Dr. Zinder said that the public trusts academic researchers, but not industry.

Dr. Gottesman stressed that under the Working Group's proposal, the IBC would make the decision on containment using the CDC document only as guidance. Dr. Goldstein said that how the IBCs use and interpret the CDC guidelines should be made more explicit, so that there are uniform standards.

Dr. McGarrity said that he is comfortable in accepting voluntary guidelines. He felt that the Working Group's background report is excellent and that perhaps an abridged version could be published for educating the general public.

Dr. Holmes said that he supports retaining the current prohibition dealing with the introduction of drug resistance traits. He said that to make the Guidelines voluntary would be a mistake and could invite legislation.

Dr. Baltimore said that the concern raised in the Boston area is not a unique situation and that activities at the Federal level are still important. He said that since there are differences in the science done at different institutions it is not surprising, and not relevant to the present discussion, that different IBCs in California operate differently. Dr. Baltimore emphasized his view that IBC prereview is a serious obstruction of science, which results in scientific momentum being lost.

Dr. McKinney pointed out that the NIH could still choose to mandate guidelines even if the RAC recommends otherwise. He suggested that reference to CDC and USDA guidelines not be incorporated into the body of the text of the revised guidelines; rather they could be cited as references.

Ms. King suggested that the RAC should structure the issues on which it wants public comment, such as treatment of prohibitions and the voluntary vs. mandatory nature of the guidelines. Dr. Talbot pointed out that the RAC could follow Ms. King's suggestion and present issues for public comment. The alternative would be for the RAC to accept the Working Group proposal, the Baltimore-Campbell proposal, or an amalgam of the two. Following the meeting, NIH staff could then develop a new version of the Guidelines based on the RAC proposal and put this out for public comment.

Dr. Harris then moved to accept the report of the Working Group so that discussion could proceed to consider the report section by section. Dr. Mason seconded the motion. There followed discussion of the effect of such a motion.

Dr. Ahmed praised the report of the Working Group. He favored publication for public comment of a series of different options. Dr. Mason expressed concern about eliminating all of the prohibitions. Dr. Saginor suggested that the RAC might first consider the Adelberg-Zinder minority proposal to abolish the Guidelines. Dr. McKinney said that he considered the Working Group's recommendations as too cursory. Dr. Gottesman responded that the Working Group had considered the issues in-depth at two meetings and had prepared a report on its evaluation of the risks associated with recombinant DNA research. The RAC could change or elaborate on the recommendations before seeking public comment. Dr. Zinder said that the recommendations of the Working Group were adopted unanimously for those concerning Part IV of the Guidelines.

Dr. Baltimore, in the interests of providing a forum for RAC discussion of the points of difference between the various proposals, moved a seven part motion as a substitute for Dr. Harris' motion:

1. Accept the first section of the Baltimore-Campbell proposal, as follows:

"Section I-A of the NIH Guidelines will be replaced with the following:

'I-A. Purpose. The purpose of these Guidelines is to specify standard practices for constructing and handling (i) recombinant DNA molecules and (ii) organisms and viruses containing recombinant DNA molecules. Adherence to these standards by all laboratories using recombinant DNA is recommended.'

2. Accept the second section of the Baltimore-Campbell proposal, as follows:

"Part I-C of the NIH Guidelines shall be eliminated."

3. Accept the second section of the Working Group proposal, as follows:

"Section I-D of the Guidelines, Prohibitions, would be eliminated."

4. Accept the third section of the Working Group report modified by removing references to CDC Guidelines and USDA Regulations and treating these references in a footnote, as follows:

"Part III of the Guidelines would be replaced with the following language:

'Part III discusses experiments covered by the Guidelines. The reader should first consult Part I, where exempt experiments are listed.

'Where recommended physical containment levels applicable to non-recombinant DNA experiments exist for either the host or the vector*, recombinant DNA experiments should be carried out at containment levels at least as high as those recommended for non-recombinant DNA experiments. If there is clear evidence that the donor DNA will significantly change the pathogenicity of the host, the containment level appropriate to the anticipated change will be applied. Otherwise, all experiments may be carried out under conditions of P1 or P1-LS physical containment.'

5. The following admonition would be added:

"No experiments should be performed which involve deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire it naturally, if such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture."

6. Accept the fourth section of the Baltimore-Campbell proposal, as follows:

*Such as those specified by CDC Guidelines or the USDA Quarantine Regulations.

"Part IV of the NIH Guidelines shall be eliminated, with the following exceptions:

"(a) Those definitions listed in Part IV-C which may be needed to clarify statements made elsewhere in the Guidelines shall be retained.

"(b) Those portions of Part IV-E defining the composition of RAC and prescribing rules for RAC procedures shall be retained.

"(c) The following statement shall be added:

"Each institution conducting or sponsoring recombinant DNA research should take responsibility for monitoring its own activities in this area. Any unusual events that might be associated with the use of recombinant DNA molecules should be reported to the Director, NIH."

7. Accept the fifth section of the Baltimore-Campbell proposal with deletion of the words "submitted in support of requests for exceptions from the prohibitions," as follows:

"Section VI of the Guidelines will be eliminated, except for those portions of Section VI-F relevant to the protection of proprietary information. "

Dr. Berns seconded the motion.

Dr. Saginor suggested an amendment to Dr. Harris' motion in the form of a policy statement that there is a continuing need for the RAC and applicable recombinant DNA guidelines. The purpose of the amendment was to indicate that the Adelberg-Zinder proposal is not being accepted. Dr. Harris agreed to the amendment.

Ms. King said she wanted the RAC to vote on replacing parts 1 and 6 of the Baltimore motion with wording from the Working Group proposal. It was suggested that votes be on one part at a time. Ms. King then moved to replace the first part of Dr. Baltimore's motion with the first section of the Working Group's proposal as follows:

"Section I-A of the Guidelines would be amended to read as follows:

"I-A. Purpose. The purpose of these Guidelines is to specify standard practices for constructing and handling (i) recombinant DNA molecules and (ii) organisms and viruses containing recombinant DNA molecules."

The motion was seconded by Dr. Goldstein. Ms. King stated that she favors retention of limited Guidelines that require IBC review, and she favors an oversight function for the RAC; she does not support self-regulation. Dr. Baltimore did not accept Ms. King's proposed amendment. Dr. Berns pointed out that the substitution Ms. King was proposing did not make much difference. The real point of contention in the RAC concerned part six of Dr. Baltimore's motion.

Ms. King withdrew her previous motion and then moved to delete part six of Dr. Baltimore's motion. If her motion were accepted, this would leave intact Part IV of the Guidelines. It was pointed out that the Working Group had proposed a change in Part IV dealing with IBC membership. Ms. King said that if her motion passed, then another perfecting motion could be introduced dealing with IBC membership. Dr. Harris seconded. The motion failed to carry by a vote of nine in favor, twelve opposed, and no abstentions.

Dr. Fedoroff noted that the motion as it stands would eliminate all prohibitions including the prohibition against deliberate release into the environment. Dr. Baltimore suggested that if the RAC wished, a statement regarding deliberate release could be included with the admonition on drug resistance. Dr. Berns said that in his view the recommendation that experiments be conducted under P1 containment precludes deliberate release into the environment.

Dr. Maas then moved to add the current prohibition on the cloning of certain toxins to the admonition on drug resistance. Dr. Goldstein seconded. Dr. Gottesman said that the cloning of toxins is an example of an area of concern. She noted that the RAC Working Group on Tbxins recommended at the last RAC meeting prohibition of cloning of certain toxin genes and that other experiments involving cloning of toxin genes should proceed only in E. coli K-12 in the absence of special review by ORDA. Dr. Baltimore agreed to accept addition of the wording regarding toxins currently in Section I-D-2 to the admonition on drug resistance and to retain Appendix G of the current Guidelines.

Dr. Ahmed moved that a working group be appointed to study the prohibitions and report back to the RAC. Dr. Goldstein seconded the motion. Dr. Mason disagreed, noting that at the last meeting a working group had been appointed to report on revision of the guidelines. They had reported, and now the RAC was working through the proposal to prepare material for public comment. The motion failed to carry by a vote of three in favor, fourteen opposed, and three absentions.

Mr. Thornton recognized Dr. Susan Wright. She said the RAC was short-circuiting long and detailed discussions it should have on all the critical issues. She asked RAC members to acknowledge ties that they might have with genetic engineering companies. She said there should be discussion of why the working group had decided to eliminate public members on IBCs. She expressed concern about the currently prohibited experiments and large-scale experiments. She

cited a report she had submitted, prepared for the Commission of the European Communities, entitled "Hazards Involved in the Industrial Use of Micro-organisms." She said that change of phenotype due to mutation and discharge of waste into the environment are important issues among many others that need to be considered before a decision is reached.

Dr. Fedoroff said that there should be flexibility to have a group look at and approve specific experiments which are otherwise admonished against. Dr. Baltimore said investigators wishing to do such experiments could come to the local IBC or the RAC to discuss conditions under which such experiments could be done.

Dr. Berns said that at a meeting of the Large Scale Review Working Group on September 9, 1981, none of the members thought that the large-scale prohibition should be retained.

Mr. Thornton recognized Ms. Claire Nader who said that the RAC should look at the assumptions behind the recommendations such as that all corporations will do the right thing, and that the technology is safe. She said that there were no experts on corporate behavior, or law enforcement, or anti-trust questions on the RAC. She said the RAC should have on it people who want to talk about risks. She criticized the way in which the RAC was proceeding.

Dr. Nightingale said that a working group on the prohibitions was appointed over a year ago and that the prohibitions have been discussed extensively before this meeting. Dr. Gottesman said that it was peculiar to be concerned about the prohibitions and at the same time recommending that the entire system become voluntary. She said that perhaps there could be a recommendation that these experiments be reviewed by the RAC.

Mr. Daloz moved that a vote be taken on Dr. Baltimore's motion, as amended. The motion to end discussion and vote failed to carry by a vote of four in favor, fourteen opposed, and three abstentions.

Dr. Ahmed said he wanted detailed procedures built into the revised Guidelines for handling the currently prohibited experiments. Dr. Baltimore said that the absence of detailed procedures pertains in the case of all nonrecombinant DNA laboratory work including that with known pathogens.

Mr. Thornton asked for a show of hands of RAC members who wished to continue discussion of this agenda item for an additional thirty minutes until approximately 3:30 p.m. The vote was eighteen in favor, one opposed.

Dr. Mason said that the RAC and the Guidelines cannot deal with scientists or industrial groups who are uninformed, dishonest, or careless. We have tried to produce guidelines that responsible people will follow. There is no way to provide for every contingency.

Dr. Holmes moved to add current prohibition I-D-4 ("Deliberate release into the environment of any organism containing recombinant DNA.") to the admonitions regarding cloning of toxins and transfer of drug resistance traits. Dr. Landy supported inclusion of I-D-4; Dr. Berns did not support it. The motion failed to carry by a vote of eight in favor, ten opposed, and two absentions.

Dr. Baltimore's amended motion was reviewed. Dr. Talbot said that if the proposal passed, the NIH staff would prepare a version of proposed revised Guidelines based on the proposal, and that it would be put in the Federal Register for public comment, along with background describing the work of the working group and the deliberations of the RAC. NIH would actively solicit comment on the proposal beyond its publication in the Federal Register.

The question was called and the vote to substitute Dr. Baltimore's motion, as amended, for Dr. Harris' motion was fifteen in favor, three opposed, and two abstentions. Dr. Ahmed asked to be recorded as voting against the motion. The motion was as follows:

"1. Section I-A of the Guidelines would be amended to read as follows:

"I-A. Purpose. The purpose of these Guidelines is to specify standard practices for constructing and handling (i) recombinant DNA molecules and (ii) organisms and viruses containing recombinant DNA molecules. Adherence to these standards by all laboratories using recombinant DNA is recommended.

"2. Section I-C of the Guidelines would be eliminated.

"3. Section I-D of the Guidelines, Prohibitions, would be eliminated.

"4. Part III of the Guidelines would be replaced with the following language:

"Part III discusses experiments covered by the Guidelines. The reader should first consult Part I, where exempt experiments are listed.

"Where recommended physical containment levels applicable to non-recombinant DNA experiments exist for either the host or the vector*, recombinant DNA experiments should be carried out at containment levels at least as high as those recommended for non-recombinant DNA experiments. If there is clear evidence that the donor DNA will significantly change the pathogenicity of the host, the containment level appropriate to the anticipated change will be applied. Otherwise, all experiments may be carried out under conditions of P1 or P1-LS physical containment.

*Such as those specified by the CDC Guidelines or the USDA Quarantine Regulations.

"5. Material would be added to Part III, as follows:

"No experiments should be performed which involve:

- "(a) Deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire it naturally, if such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture.
- "(b) Deliberate formation of recombinant DNAs containing genes for the biosynthesis of toxins lethal for vertebrates at an LD₅₀ of less than 100 nanograms per kilogram body weight (e.g., the botulinum toxins, tetanus toxin, diphtheria toxin, Shigella dysenteriae neurotoxin). Guidelines for the cloning of DNAs containing genes coding for the biosynthesis of toxins which are lethal to vertebrates at 100 nanograms to 100 micrograms per kilogram body weight are specified in Appendix G.

"6. Part IV of the Guidelines would be eliminated with the following exceptions:

- "(a) Those definitions listed in Part IV-C which may be needed to clarify statements made elsewhere in the Guidelines shall be retained.
- "(b) Those portions of Part IV-E defining the composition of RAC and prescribing rules for RAC procedures shall be retained.
- "(c) The following statement shall be added:

"Each institution conducting or sponsoring recombinant DNA research should take responsibility for monitoring its own activities in this area. Any unusual events that might be associated with the use of recombinant DNA molecules should be reported to the Director, NIH.

"7. Section VI of the Guidelines will be eliminated, except for those portions of Section VI-F relevant to the protection of proprietary information."

The vote on this substitute motion was called, and the vote was sixteen in favor, three opposed, and one abstention.

Dr. Zinder requested that a motion be introduced in support of the Adelberg-Zinder proposal to eliminate the Guidelines and the RAC. No motion was introduced.

Mr. Thornton noted that RAC had approved a proposed revision of the Guidelines for publication in the Federal Register, with the understanding that the committee would subsequently review that document and any comments generated by it at the next RAC meeting.

IV. PROPOSED AMENDMENT OF SECTION III-C-2-a AND ADDITION OF NEW SECTION III-C-7-c

Mr. Thornton asked Dr. Berns to initiate discussion of the proposal (tabs 1026, 1035/9) from Dr. Lois Miller of the University of Idaho. Dr. Berns said that Dr. Miller requests a modification of Section III-C-2-a of the Guidelines. This modification would permit invertebrate viruses to be treated as animal viruses are currently treated under the NIH Guidelines. Dr. Miller also proposed that a new Section III-C-7-c be added to the Guidelines. Section III-C-7-c would read:

"III-C-7-c. Transfer to Invertebrates. DNA from any nonprohibited source [Section I-D], except for greater than one quarter of a eukaryotic viral genome, which has been cloned and propagated in E. coli K-12, may be transferred with the E. coli vector used for cloning to any eukaryotic cells in culture or to any invertebrate organism and propagated under conditions of physical containment comparable to P1 and appropriate to the organism under study [2A]. Transfers to any other host will be considered by the RAC on a case-by-case basis [45]."

Dr. Berns asked if there are any reasons for not treating invertebrate viruses the same as animal viruses under the Guidelines. Mr. Thornton asked if containment problems for insects are of significance in relation to this proposal. Dr. Talbot said that this consideration is relevant to proposed Section III-C-7-c; this section would deal with introducing cloned DNA into insects. The proposed modification of Section III-C-2-a would affect the treatment of invertebrate viruses in tissue culture systems. Dr. Berns said he had discussed questions of containment with Dr. Tobin of the United States Department of Agriculture (USDA), who said that she saw no problem with the proposal as written.

Dr. Berns moved acceptance of the proposal to amend Section III-C-2-a and to add a new Section III-C-7-c to the Guidelines. Dr. Fedoroff seconded the motion. By a vote of eleven in favor, none opposed, and five abstentions the RAC adopted the motion.

Revised Section III-C-2 would read as follows:

"III-C-2. Invertebrate Host-Vector Systems.

"III-C-2-a. Invertebrate Viral Vectors. Experiments involving invertebrate virus vectors can be done as follows:

"III-C-2-a-(1). Recombinant DNA molecules containing no more than two-thirds of the genome of any invertebrate virus [all viruses from a single Family (36) being considered identical (50)] may be propagated and maintained in cells in tissue culture using P1 containment. For such experiments, it must be shown that the cells lack helper virus for the specific Families of defective viruses being used. The DNA may contain fragments of the genomes of viruses from more than one Family but each fragment must be less than two-thirds of a genome.

"III-C-2-a-(2). Recombinants with less than two-thirds of the genome of any invertebrate virus may be rescued with helper virus using P2 containment unless it is classified by the CDC as a class 3 agent (1) in which case P3 containment is required.

"III-C-2-a-(3). Experiments involving the use of other whole or defective virus genomes to propagate DNA sequences from prokaryotic or eukaryotic organisms (and viruses), or as vectors to transform non-permissive cells, will be evaluated by NIH on a case-by-case basis [45] and will be conducted under the prescribed physical and biological containment conditions. (See Section IV-E-1-b-(3)-(c).)"

"NIH will also review on a case-by-case basis [45] all experiments involving the use of virus vectors in animals and will prescribe the physical and biological containment conditions appropriate for such studies. (See Section IV-E-1-b-(3)-(c).)"

V. REQUEST TO CLONE SUBGENOMIC SEGMENTS OF RIFT VALLEY FEVER VIRUS

Dr. Berns introduced the request (tabs 1030, 1035/4, 1038) of Molecular Genetics, Inc., of Minnetonka, Minnesota, to clone, under P1 containment conditions, segments of the Rift Valley Fever Virus genome. The objective is to clone the segments which encode the virus' antigenic determinants. The work would be performed in collaboration with the U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Maryland.

Dr. Berns said Rift Valley Fever Virus is a major problem in cattle in Africa. The virus may have recently extended its range into Egypt and the Sinai Peninsula. Work with the virus in the United States is prohibited by the USDA, except under special conditions. In addition to being a significant agricultural problem, the virus may be transmitted to humans.

The virus itself is a negative stranded RNA virus. Such viruses are not infectious when purified as the complementary strand is needed to function as a messenger. The Rift Valley Fever Virus genome is segmented; the genome is composed of three separate pieces of RNA. The investigators propose to work with one of the three segments, the so-called "M" or medium sized segment which codes for those of the virus' antigenic determinants that elicit neutralizing antibodies. He said that the issues are comparable to those

with the cloning of Foot and Mouth Disease Virus. However, the Rift Valley Fever Virus project provides more safeguards because the virus genome is negative stranded, segmented RNA. Dr. Berns said he felt P1 containment would be adequate for the project.

Dr. Baltimore agreed with Dr. Bern's evaluation, and added two points. He said that the proposed method of reverse transcription, the "snap-back" procedure, would ensure that the full RNA is not cloned. He cautioned, however, that Rift Valley Fever Virus is a Bunyavirus and Bunyaviruses are known to recombine within the family. He suggested that the laboratory work areas be limited to research with Rift Valley Fever Virus and that investigators not simultaneously study other Bunyaviruses. Dr. Pilacinski of Molecular Genetics, Inc., said that the company is not presently working with Bunyaviruses other than Rift Valley Fever Virus and has no plans to do so in the near future.

Dr. Baltimore moved approval of the proposal at the P1 level of containment with the stipulation that other Bunyaviruses not be studied in the same laboratory areas and that the "snap-back" procedure, as described in the protocol, be utilized to generate the DNA. Dr. Berns seconded the motion.

Mr. Thornton called the vote. By a vote of sixteen in favor, none opposed, and two abstentions, the RAC adopted the motion.

VI. STATEMENT ON THE PROPOSED REVISION OF THE GUIDELINES

Mr. Thornton asked that his statement concerning agenda item III, "Proposed Revision of the Guidelines," be distributed (Attachment V). He said that to have made this statement before consideration of the issue could have compromised his position as chairman. However, he felt it was now appropriate to distribute the statement.

VII. CLOSED SESSION

The RAC went into closed session to consider proposals involving proprietary information from commercial concerns for scale-up of recombinant DNA experiments.

VIII. PROPOSED AMENDMENT OF SECTION III-O-2

Mr. Thornton asked Dr. Talbot to discuss the proposal (tabs 1025, 1035/6) of Dr. Michael J. Ross of Genentech, Inc. Dr. Talbot said Dr. Ross had requested an amendment of Section III-B-3 of the Guidelines. Section III-B-3 currently specifies that the Director, NIH, may set containment levels, after a case-by-case review, for certain experiments involving non-HV1 prokaryotic host-vector systems. Dr. Ross proposed to amend the Section to permit the cloning of DNA from any nonpathogenic species in nonpathogenic lower eukaryotes at P3 containment and into nonpathogenic prokaryotes at the P2 level of containment.

Dr. Talbot said that modification of Section III-B-3 is not the appropriate way to make the changes Dr. Ross proposes, since Section III-B-3 deals only with prokaryotes. Dr. Talbot suggested that Section III-O-2, "Experiments Involving Prokaryotes Nonpathogenic for Man, Animals, or Plants and/or Lower Eukaryotes Nonpathogenic for Man, Animals, or Plants" could appropriately be modified to reflect Dr. Ross' intent.

Dr. Fedoroff noted that Dr. Ross' proposal would change the current Section III-O-2 in two ways: it would allow cloning of DNA from nonpathogenic higher eukaryotes; and it would lower the level for cloning in nonpathogenic prokaryotes from P3 to P2. Dr. Fedoroff moved acceptance of the proposal.

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

Section III-O-2 would be amended to read as follows:

"III-O-2. Experiments Involving Nonpathogenic Prokaryotic and Lower Eukaryotic Host-Vector Systems. DNA from any species nonpathogenic for man, animals, or plants may be cloned into lower eukaryotes nonpathogenic for man, animals, or plants at the P3 level of containment [2A]. DNA from any species nonpathogenic for man, animals, or plants may be cloned into prokaryotes nonpathogenic for man, animals, or plants at the P2 level of containment [2A]. Data supporting the contention that the donor and recipient are nonpathogenic must be submitted to the local IBC. Lower levels of physical containment may be assigned by ORDA on a case-by-case basis for specific donor-recipient combinations. (See Section IV-E-1-b-(3)-(h).)"

IX. PROPOSED AMENDMENT OF SECTION I-D-6

Dr. McKinney opened discussion of the proposal (tabs 1027, 1035/5) by Dr. Irving Johnson of Eli Lilly and Company to amend Section I-D-6 of the Guidelines as follows (modified language underlined):

"I-D-6. Large-scale experiments [e.g. more than 10 liters of culture] with organisms containing recombinant DNAs other than those listed in Appendix C, Paragraphs 2, 3, and 4 of the Guidelines, unless the recombinant DNAs are rigorously characterized and the absence of harmful sequences established (3). (See Section IV-E-1-b-(3)-(d).)"

The text in Appendix C dealing with large-scale experiments in Paragraph 2 (E. coli K-12 host-vector systems), Paragraph 3 (S. cerevisiae host-vector systems), and Paragraph 4 (B. subtilis host-vector systems) would be replaced with the following revised text:

"Large-scale experiments (e.g. more than 10 liters of culture) require prior IBC review and approval."

This modification would delegate authority to the IBC to review proposals and set containment for large-scale procedures when certain E. coli K-12, B. subtilis and S. cerevisiae host-vector systems are used. Large-scale procedures employing other host-vector systems would continue to be reviewed by RAC and approved by the NIH.

Dr. McKinney said that the majority of requests for exceptions to the 10 liter limit have been submitted by industry. Dr. McKinney felt that industry's response to Part VI, Voluntary Compliance, of the Guidelines has been responsible. He suggested that Dr. Johnson's proposal would serve to improve operating conditions, both at the research and industrial level, and facilitate large-scale production utilizing E. coli K-12, B. subtilis or S. cerevisiae host-vector systems. He moved adoption of the proposal.

Dr. McGarrity said he had reviewed the September 2 letter submitted to the RAC by Dr. Susan Wright as well as the attached report entitled "Hazards Involved in the Industrial Use of Microorganisms." The latter report was contracted for by the Commission of the European Communities (CEC) to evaluate the hazards involved in the industrial development, production and use of microbial cells and their products.

Dr. McGarrity addressed the criticisms Dr. Wright raised against Dr. Johnson's proposal. Dr. McGarrity agreed with Dr. Wright that the statement "the principle of the absence of increased risk with increased volume has been accepted by the RAC," as advanced by Dr. Johnson is inaccurate. He said Dr. Johnson draws a broader conclusion than is warranted from the decision at the June 1980 RAC Meeting to delete a sentence from Section I-D-6. However, he said that since June 1980 there have been many developments which indicate a modification in RAC's view. For example, in September 1980, RAC delegated the responsibility of reviewing physical facilities for large-scale experiments to the local IBCs.

In another criticism, Dr. Wright stated "that the British Genetic Manipulation Advisory Group (GMAG) is to consider in late September a proposal from the Confederation of British Industry (CBI) to weaken the British controls for large-scale work should not be used to justify the Lilly proposal." She further stated that ". . . it is not at all clear that GMAG will take the 'positive action' which Dr. Johnson anticipates." Dr. McGarrity said he agreed with Dr. Wright that the RAC should not be influenced in its decisions by possible decisions GMAG may take.

In other criticisms, Dr. Wright asserts "the fact that 'no unforeseen difficulties have been encountered' when the industry has operated under controls involving prior review cannot be used to justify the claim that no

problems will arise when controls are removed." She further stated that "no comparative studies of the risks of small- and large-scale work have been carried out, and any statements comparing these risks are developed against a background of very wide uncertainty." She refers to several concerns raised in the CEC report.

Dr. McGarrity said that the CEC report raises concerns but also states that industrial fermentation processes are unlikely to be contaminated because fermentation failure is a very expensive problem. To be productive, fermentors must operate almost continuously. He said these economic facts argue for strong quality control measures in industry. Dr. McGarrity added that the authors of the CEC report were "impressed by the well documented care" taken by the industry "to ensure the wholesomeness of their products." Dr. McGarrity said that the CEC report tends to support Dr. Johnson's position rather than Dr. Wright's. Dr. McGarrity then seconded Dr. McKinney's motion for approval.

Mr. Thornton then recognized Dr. Wright. She said that the CEC report is the only report that has been written on the hazards of the industrial uses of genetic biotechnology. She said that the CEC report states: (1) that the scale of the use of microorganisms is going to expand so greatly that this area should be carefully examined, and (2) this work should be regulated. She said she was not convinced by Dr. McGarrity's arguments and said the RAC has not yet addressed several areas of serious concern.

Mr. Thornton then recognized Dr. Max Marsh of Eli Lilly and Company. Dr. Marsh noted that Dr. Wright's September 2 letter states that Dr. Johnson's proposal "would exempt large-scale work involving E. coli K-12, Saccharomyces cerevisiae, Bacillus subtilis, and any other host-vector system listed in Appendix C of the Guidelines." Dr. Marsh pointed out that Dr. Wright is incorrect in claiming this would extend to "any other host-vector system." Dr. Johnson's proposal was very specific as to the three specified host-vector systems which would be covered by this amendment.

In addition, Dr. Marsh pointed out that a continuous fermentation operation is a very complex process which is computer controlled. It is very easy with the continuous monitoring utilized to detect contamination.

Dr. Miller of FDA said that both the consuming public and the biotechnology industry would be served by this change in Section I-D-6.

Dr. Saginor said that since this proposal would delegate responsibility to IBCs, he wanted to mention for the record his concern that IBCs be kept in place, in relation to agenda item III considered earlier in the meeting.

Dr. Berns pointed out that industry currently complies with the NIH Guidelines voluntarily; there is no mandatory requirement for industrial firms to institute IBCs. Dr. McKinney concurred but added that industry is complying out of self-interest as well as public interest. In view of RAC's experience with these three host-vector systems, he said the committee should recommend Dr. Johnson's proposal.

Mr. Thornton called the vote. By a vote of eleven in favor, two opposed, and one abstention, the RAC adopted the proposal.

X. PROPOSAL TO INCLUDE STREPTOCOCCUS PYOGENES ON SUBLIST F OF APPENDIX A

Mr. Thornton asked Dr. Maas to begin discussion of the proposal (tabs 1028, 1035/8) from Dr. Joseph Ferretti of the University of Oklahoma Health Sciences Center to include Streptococcus pyogenes on sublist F of Appendix A. In support of his request, Dr. Ferretti submitted evidence demonstrating genetic exchange between Streptococcus pyogenes and Streptococcus sanguis. Streptococcus sanguis is currently included in sublist F.

Dr. Maas said the data demonstrate genetic exchange between S. pyogenes and S. sanguis. These exchanges occur primarily through transformation and conjugation with plasmids. Dr. Maas felt the request was reasonable and moved approval. Dr. Fedoroff seconded the motion.

Dr. Goldstein asked if Streptococcus pyogenes is implicated in rheumatic fever. Dr. Maas replied that it was. However, it was agreed that S. pyogenes merited inclusion on Sublist F of Appendix A on the basis of exchange data.

Mr. Thornton called for the vote on the motion. By a vote of fourteen in favor, none opposed, and no abstentions, the RAC adopted the proposal.

XI. REQUEST TO PERMIT ONE-WAY TRANSFER OF STREPTOCOCCUS LACTIS DNA INTO S. SANGUIS AND TO PERMIT TRANSFER OF A RECOMBINANT PLASMID FROM S. FAECALIS TO S. LACTIS

Dr. Fedoroff introduced the request (tabs 1029, 1035/3) of Dr. Larry McKay of the University of Minnesota for permission to transfer Streptococcus lactis DNA into Streptococcus sanguis strain Challis. Dr. McKay also requested that these strains be included in Appendix A on the basis that they exchange genetic information by known physiological processes. In addition, he requested permission to transfer a recombinant plasmid from S. faecalis to S. lactis.

Dr. Fedoroff noted that Dr. McKay wishes to reduce S. lactis plasmids in size with endonucleases in order to obtain the smallest functional plasmid. He would then purify the plasmid, transfer it to Streptococcus sanguis by transformation, transfer it by conjugation from S. sanguis to S. faecalis, and return it to S. lactis from S. faecalis by conjugation.

Dr. Fedoroff asked if organisms have been included in Appendix A of the Guidelines on the basis of data demonstrating unidirectional transformation. Dr. Gartland said organisms had been included in Appendix A on that basis.

Dr. Fedoroff, on the basis of the data submitted, moved approval of the requests as written. Dr. McGarrity seconded the motion.

Dr. Ahmed requested a clarification of the motion; he asked if S. lactis and S. sanguis would be placed on an existing sublist of Appendix A or if a new sublist would be created. Dr. Gartland asked Dr. Fedoroff whether the submitted evidence justifies including S. lactis in Sublist F of Appendix A. Dr. Fedoroff said the evidence supports one way transformation of S. sanguis by S. lactis DNA, but not the reverse. Dr. Talbot suggested, therefore, that Sublist E of Appendix A might appropriately be amended to permit transformation of S. sanguis by S. lactis DNA. A new entry could also be added to Appendix E to permit transfer of a recombinant plasmid from S. faecalis to S. lactis by conjugation. By a vote of fourteen in favor, none opposed, and no abstentions, the RAC approved these actions.

XII. REQUEST TO CLONE SACCHAROMYCES CEREVISIAE DNA IN SALMONELLA TYPHIMURIUM

Dr. Pinon introduced the request (tabs 1031, 1035/5, 1039) of Drs. Christopher Marvel and Edward Penhoet of the University of California, Berkeley, to clone Saccharomyces cerevisiae DNA in Salmonella typhimurium, using a nonmobilizable plasmid (YEpl3).

Dr. Pinon noted that S. typhimurium is a CDC Class 2 etiological agent, but the investigators will employ attenuated strains. Furthermore, DNA from S. cerevisiae, a nonpathogen, will be introduced. Dr. Pinon recommended that the investigators be permitted to proceed under P1 containment conditions. Dr. Maas concurred and moved acceptance of the request. Dr. Pinon seconded the motion.

Dr. Ahmed asked why Drs. Marvel and Penhoet suggest they might be willing to employ P3 containment conditions. Dr. Landy said he did not feel willingness to employ high containment indicated the investigators have concerns on the safety of the experiments, but rather an eagerness to begin the research and a willingness to work under RAC imposed conditions.

Mr. Thornton called the question. By a vote of fourteen in favor, none opposed, and no abstentions, RAC adopted the motion to permit Drs. Marvel and Penhoet to proceed under P1 containment conditions.

XIII. REQUEST TO UTILIZE HEMOPHILUS PARAINFLUENZAE TO CLONE MOLONEY MURINE LEUKEMIA PROVIRUS

Dr. Berns began discussion of the proposal (tabs 1032, 1035/1, 1036) of Dr. James W. Gautsch of Scripps Clinic and Research Foundation to clone Moloney MuLV provirus and cellular flanking regions in Hemophilus parainfluenzae. The provirus DNA and flanking regions will be ligated into vector pRK290, a plasmid with a broad host range in gram negative bacteria. The cloned plasmid will subsequently be used to infect NIH 3T3 cells. Dr. Berns said the investigators wish to study the effect of methylation of DNA on RNA transcription.

Dr. Berns said H. parainfluenzae is part of the normal flora of the human upper respiratory tract. The investigators are thus inserting the MuLV provirus into a bacterium which could colonize a laboratory worker. He noted, however, that Moloney MuLV virus is classified by the National Cancer Institute as a low risk virus. The normal host is the mouse, and the virus is not known to function in any other organism. Should the recombinant DNA-containing H. parainfluenzae lyse in the respiratory tract of a colonized individual, the MuLV DNA would be presented to the cells of the respiratory tract as uncoated DNA, not as the whole virus. This is not the optimal manner in which to transfect cells. Dr. Berns said that he feels the risk is miniscule and recommended that the experiment be permitted at the P2 level of containment.

Dr. Goldstein asked what the host range of the MuLV virus was in tissue culture. Dr. Berns replied that MuLV is classified as an ecotropic virus, i.e., mouse-tropic. Dr. Goldstein asked how that classification was generated; was the test performed in tissue culture systems using whole virus? Dr. Berns replied that is was.

Dr. Berns moved that the experiments be permitted at the P2 level of containment. Dr. McKinney seconded the motion. By a vote of eleven in favor, none opposed, and three abstentions, the RAC adopted the motion.

XIV. DEVELOPMENT OF HOST-VECTOR SYSTEM BASED ON CORYNEBACTERIUM GLUTAMICUM

Dr. Maas introduced the request (tabs 1033, 1035/11) of Dr. Daniel Liberman of the Massachusetts Institute of Technology. Dr. Liberman requested containment conditions be established for the development of a host-vector system based on the gram positive bacterium Corynebacterium glutamicum. Corynebacterium glutamicum would be used as the host; three types of plasmids including hybrid plasmids would be tested for use as vectors. Dr. Maas said Corynebacterium glutamicum is not a pathogen and P1 containment should be adequate.

Dr. Goldstein asked if the proposed plasmid vectors carry drug resistance genes. Dr. Maas replied that some did. Dr. Goldstein pointed out that although Corynebacterium glutamicum is not a pathogen, it is related to the organism causing diphtheria.

Dr. Ahmed asked if this proposal might violate a prohibition in that drug resistance traits would be introduced into a nonpathogenic organism, which might transfer drug resistance traits to pathogens. Dr. Maas suggested that use of non-conjugative, poorly-mobilizable plasmids could be required. He said this restriction would address concerns about transfer of genetic information from Corynebacterium glutamicum to pathogenic Corynebacteria that live on the human skin. Mr. Thornton asked Dr. Liberman to comment on the effect this restriction might have on the project. Dr. Liberman thought the restriction would not seriously affect the protocol.

Dr. Maas moved approval of the proposal under P1 containment conditions provided that nonconjugative, poorly mobilizable plasmids are used as vectors. By a vote of eleven in favor, one opposed, and one abstention, RAC adopted the motion.

Dr. Liberman asked if RAC might rule in general on the use of Class 1 agents in the development of novel host-vector systems. Dr. Talbot pointed out that Dr. Liberman's request as published in the Federal Register had dealt only with Corynebacterium glutamicum; a more general statement on all Class 1 agents had not appeared in the Federal Register and thus could not be acted on. Dr. Talbot drew attention to the action adopted by RAC earlier in the meeting concerning modification of Section III-O-2, as this partially addressed Dr. Liberman's concern.

XV. PROPOSED USE OF CONJUGATIVE PLASMIDS TO TRANSFER DNA BETWEEN E. COLI, VIBRIO CHOLERA, AND VIBRIO HARVEYI

Dr. Maas initiated discussion of the request (tabs 1037, 1035/2) from Dr. J. W. Hastings of Harvard University for permission to clone Vibrio harveyi DNA in E. coli and in Vibrio cholera. Conjugation proficient plasmids (e.g., pRK290 derivatives) would be used to transfer the cloned V. harveyi DNA among E. coli, V. cholera and V. harveyi. Dr. Hastings would employ an E. coli host-vector system to select V. harveyi bioluminescence genes. He would subsequently return the bioluminescence genes to V. harveyi by first transferring the genes from E. coli to V. cholera, and then transferring the genes from V. cholera to V. harveyi. He chose this method as the frequency of plasmid transfer from E. coli to V. harveyi is very low.

Dr. Maas said V. cholera is classified by the CDC as a Class 2 etiological agent. He suggested that the experiments be permitted at P1 containment, with the exception of those experiments involving V. cholera, which would be set at P2. He so moved. Dr. McKinney seconded the motion.

Dr. McGarrity noted that V. cholera exchanges genetic information with E. coli; he questioned why V. cholera is not included in Sublist A of Appendix A. Dr. Talbot said Sublist A was originally instituted as a restrictive list and inclusion of V. cholera in Appendix A has not been requested.

Dr. McGarrity asked whether P2 containment conditions were necessary. Dr. Gottesman pointed out that the investigator would employ a mobilizable plasmid which may contain DNA homologous to the V. cholera chromosome. In such a situation concern over the possible transfer of the cholera toxin gene justifies P2 containment conditions.

By a vote of ten in favor, none opposed, and three abstentions the RAC adopted Dr. Maas' motion.

XVI. CONTAINMENT CONDITIONS FOR CLONING AND EXPRESSION OF DNA CODING FOR DIPHThERIA TOXIN

Dr. Gartland initiated the discussion (tabs 1035/10, 1041) by recounting the history of the proposal submitted by Dr. John Murphy of Harvard Medical School. Dr. Gartland said Dr. Murphy requested that RAC, at its April 23-24, 1981 meeting (Minutes of the Meeting, page 28-29), consider a proposal to clone, in E. coli K-12, the 3.9 kb Bam restriction fragment of Coryneophage Beta carrying the diphtheria toxin structural gene. At that meeting, RAC set containment for the project at P4 with the experiments to be performed in high containment Building 550 at the Frederick Cancer Research Center (FCRC). The NIH subsequently accepted this recommendation. Dr. Gartland said Dr. Murphy, in a letter dated July 11, 1981, now requested greater flexibility in the setting of containment levels. Dr. Murphy proposed that the National Institutes of Health (NIH) Institutional Biosafety Committee (IBC) be delegated authority to specify laboratory and containment practices for the work to be done in high containment Building 550 at FCRC.

Dr. McKinney said that the P3 laboratories in Building 550 are served by the same water supply, waste treatment system, and ventilation system as the P4 facility. The secondary barriers, thus, afford higher than P3 containment. They are more than adequate to contain the proposed experiments. In addition, a precedent for lowering containment when the high risk portion of the experiment is completed was set with the first risk assessment experiments performed at FCRC by Dr. Malcolm Martin. Dr. McKinney suggested RAC specify that the work be conducted in P3 laboratories in Building 550 of the Frederick Cancer Research Center under conditions specified by the local IBC.

Dr. Maas requested a clarification of the experimental protocol. Dr. Talbot said Dr. Murphy intends to use Building 550 at all times, but would not use the Class III glove boxes in all experiments. Dr. Gottesman asked whether workers, trained in P4 procedures, would assist in the experiments. Dr. McKinney replied that NIAID assigns a permanent, highly competent staff to Building 550 to assist investigators. Dr. Fedoroff seconded Dr. McKinney's motion.

By a vote of eleven in favor, none opposed, and three abstentions, the RAC recommended that permission be granted to clone in E. coli K-12, in high containment Building 550 at the Frederick Cancer Research Center, restriction

fragments of Corynephage Beta carrying the structural gene for diphtheria toxin. Laboratory practices and containment equipment are to be specified by the IBC.

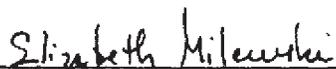
XVII. CONSIDERATION OF FUTURE MEETING DATES

Dr. Gartland's secretary will telephone all members of the RAC to arrange the date for a meeting in April or May 1982, subsequent to the next planned meeting in January 1982.

XVIII. ADJOURNMENT

Mr. Thornton expressed his appreciation to the committee for the fine manner in which business was conducted. He then adjourned the meeting at 10:30 a.m., September 11, 1981.

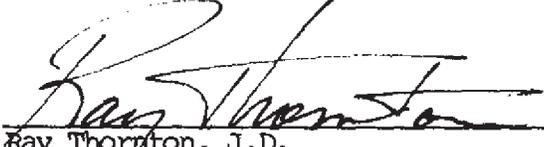
Respectively submitted,


 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.

4/12/82
 Date


 Ray Thornton, J.D.
 Chairman
 Recombinant DNA Advisory Committee