

DRAFT

1315

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

- - -

RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING

September 21, 1987

TABLE OF CONTENTS

I. CALL TO ORDER AND INTRODUCTORY  
REMARKS . . . . . 4

II. APPROVAL OF THE MINUTES OF THE  
FEBRUARY 2, 1987, MEETING . . . . . 4

III. REPORT FROM THE HUMAN GENE THERAPY  
SUBCOMMITTEE. . . . . 5

IV. PROPOSAL TO ADD BACILLUS STEAROTHERMOPHILIS  
TO APPENDIX C-V . . . . . 7

V. PROPOSAL TO AMEND SECTION I-C OF  
THE NIH GUIDELINES. . . . . 8

VI. PROPOSAL TO AMEND NIH GUIDELINES TO  
REFER SPECIFICALLY TO RESEARCH WITH  
PLANTS AND ANIMALS. . . . . 17

VII. RECOGNITION OF RETIRING COMMITTEE  
MEMBERS . . . . . 27

VIII. CONTINUATION OF PROPOSAL TO AMEND NIH  
GUIDELINES TO REFER SPECIFICALLY TO  
RESEARCH WITH PLANTS AND ANIMALS. . . . . 28

IX. FUTURE MEETING DATES. . . . . 39

Attachment: Recombinant DNA Advisory  
Committee Roster

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

RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING<sup>1</sup>

September 21, 1987

The Recombinant DNA Advisory Committee (RAC) was convened for its thirty-seventh meeting at 9:00 a.m. on September 21, 1987, in Building 31C, Conference Room 6, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892. Mr. Robert Mitchell (Chair), Attorney at Law in California, presided. In accordance with Public Law 92-463, the meeting was open to the public. The following were present for all or part of the meeting:

Committee members:

Donald C. Carner	Wolfgang K. Joklik	Jeffrey W. Roberts
Don Bert Clewell	Edward L. Korwek	Anne K. Vidaver
Mitchell L. Cohen	Robert E. Mitchell	LeRoy Walters
Bernard D. Davis	Gerald L. Musgrave	Anne R. Witherby
Charles J. Epstein	Paul E. Neiman	William J. Gartland, Jr.
Robert P. Erickson	Thomas P. Pirone	(Executive Secretary)
Susan K. Gottesman	David Pramer	
Irving S. Johnson	Fred Rapp	

A committee roster is attached (Attachment).

Ad hoc consultants:

Nina V. Fedoroff, Carnegie Institution of Washington  
Stephen H. Hughes, Frederick Cancer Research Facility  
Gerard J. McGarrity, Coriell Institute for Medical Research  
John Richardson, Emory University

Liaison representative:

Daniel P. Jones, National Endowment for the Humanities

-----  
<sup>1</sup>The RAC is advisory to the National Institutes of Health (NIH), and its recommendations should not be considered as final or accepted. The Office of Recombinant DNA Activities should be consulted for NIH policy on specific issues.

Non-voting agency representatives:

Joel M. Dalrymple, Department of Defense  
Bernard Greifer, Department of Commerce  
Phillip Harriman, National Science Foundation  
Morris A. Levin, Environmental Protection Agency  
Elizabeth Milewski, Environmental Protection Agency  
Henry Miller, Food and Drug Administration  
George P. Shibley, Department of Agriculture  
Edwin Shykind, Department of Commerce  
Sue Tolin, Department of Agriculture

National Institutes of Health staff:

Marianne Abbs, NIAID  
W. French Anderson, NHLBI  
Stanley Barban, NIAID  
Thomas C. Cloutier, OD  
Arlene Klotzko, OD  
Becky Lawson, NIAID  
Rachel Levinson, OD  
Donald M. Ralbovsky, OD

Others:

Pete Anderson, Beveridge & Diamond  
Doris Balinski, Department of Agriculture  
Manuel Barbeito, Department of Agriculture  
David Berkowitz, Department of Agriculture  
Fred Betz, Environmental Protection Agency  
Carter Blakey, Federation of American Societies for  
Experimental Biology  
Irene Brandt, Eli Lilly and Company  
Alice J. Caddow, Genencor, Inc.  
Chia Ting Chen, Department of Labor  
Joseph Chen, Department of Agriculture  
Martha F. Cleveland, American Society for Cell Biology  
Beth A. Concoby, Genencor, Inc.  
Theodore J. DeLoggio, Pennwalt Corporation  
Machi Dilworth, Department of Agriculture  
George Duda, Department of Energy  
Charles J. Eby, Hill and Knowlton  
Peter Farnham, American Society of Biological Chemists  
Gershon W. Fishbein, Genetic Engineering Letter  
Joseph R. Fordham, Novo Laboratories, Inc.  
Jeffrey L. Fox  
Bob Frederick, Environmental Protection Agency  
Stacey Frost, Department of Agriculture  
David E. Giamporcaro, Nash, Railsback, & Plesser  
Alan R. Goldhammer, Industrial Biotechnology Association  
Carol Lax Hoerner, Genentech, Inc.  
Diane Hoffman, University of Maryland

Michael Hyer, StenoTech, Inc.  
Andrea T. Jeffrey, BioTechnica International, Inc.  
Dorothy Jessup, Department of Agriculture  
Daniel D. Jones, Department of Agriculture  
Atilla T. Kadar, Food and Drug Administration  
Geoffrey M. Karny, Dickstein, Shapiro, & Morin  
John H. Keene, Abbott Laboratories  
Stanley J. Kostka, Crop Genetics International  
Pamala Love, Department of Agriculture  
Cheryl Martin, Blue Sheet  
James H. Maryanski, Food and Drug Administration  
Ronald B. Myers, NutraSweet Company  
Robert B. Nicholas, Nash, Railsback, & Plesser  
Sharon Pardo, Crop Genetics International  
John H. Payne, Department of Agriculture  
Charles Peng, Coordination Council for North American Affairs  
Stephen Poe, Department of Agriculture  
H. G. Purchase, Department of Agriculture  
Rex Rhein, McGraw-Hill World News  
Mark Rhodes, National Science Foundation  
Jeremy Rifkin, Foundation on Economic Trends  
Leslie Roberts, Science  
Edward Lee Rogers, Attorney, Washington, D.C.  
Nina M. Siegler, Bradley & Company  
Masami Shimizu, The Nihon Keizai Shimbun (Japan Economic Journal)  
Alan Shipp, Association of American Medical Colleges  
Janet Shoemaker, American Society for Microbiology  
Harriet Smith, Department of Agriculture  
Paul Stern, University of Florida  
Irene Stith-Coleman, Library of Congress  
Robert Strausberg, Genetex Corporation  
Clarence E. Styron, Monsanto Company  
William Szkrybalo, Pharmaceutical Manufacturers Association  
Laura Tangley, Bioscience  
Joseph Van Houten, Schering-Plough Corporation  
Robert Wachbroit, University of Maryland, College Park  
John Whalen, National Institute of Occupational Safety and Health  
Frederick Witherby  
Beth Workman, Manning, Selvage, & Lee

## I. CALL TO ORDER AND INTRODUCTORY REMARKS.

Mr. Mitchell, Chair, called the meeting of the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) to order at 9:00 a.m., September 21, 1987. He said the meeting was called pursuant to a Federal Register notice which, being 30 or more days prior to today's date, met requirements of the NIH Guidelines for Research Involving Recombinant DNA Molecules. He stated that the meeting would remain open to the public for its entirety, and that he expected the meeting to conclude within one day.

Mr. Mitchell asked Dr. Gartland if a quorum was present and Dr. Gartland assured the Chair that a quorum was in attendance.

Mr. Mitchell noted that he intended to make every effort to abide by the distributed agenda with respect to time estimates for each item of business. He reminded the committee that in recognizing persons for comments he would use the following order: primary and secondary reviewers on each item as set forth in the agenda; other members of RAC; ad hoc consultants to the RAC; NIH staff members; members of the public who had submitted written comments; and finally, other members of the public. He underlined that RAC was advisory to the Director of NIH; and in light of this, persons with minority opinions should voice them so as to provide Dr. Wyngaarden with the entire spectrum of opinions on a given topic. Mr. Mitchell then told the committee that in all voting he would call first for the affirmative, then for the negative, and finally for abstentions. He underlined that if any voting member felt compelled to abstain due to conflict of interest, that such member should notify the Chair so that the record could duly reflect such.

Mr. Mitchell then made note of Mailings I and II which were sent to members prior to the meeting. He also noted that the recently received materials were supplied at the table for each member.

Mr. Mitchell said that the reason the June meeting had been cancelled was that the RAC Working Group on Revision of the Guidelines had not finished its work on the proposed addition of plant and animal containment to the NIH Guidelines. He then introduced the four ad hoc consultants: Drs. Stephen Hughes, John Richardson, Nina Fedoroff and Gerard McGarrity.

## II. APPROVAL OF THE MINUTES OF THE FEBRUARY 2, 1987, MEETING.

Mr. Mitchell called on Dr. Musgrave to report on the minutes of the February 2, 1987, meeting of the RAC. Dr. Musgrave said he

had reviewed the minutes, and they appeared to be substantially correct and moved their adoption.

Dr. Walters seconded the motion and added that he believed three minor corrections to the minutes were in order. The first correction to be made was on page 4 of the minutes, and Dr. Walters suggested the wording, "public members having previously submitted written documents" be replaced with "members of the public who had submitted written documents." The second correction was on page 6, where Dr. Walters suggested that the clause, "covering respectively animals, microorganisms other than vaccines and vaccines," should be reworded to "covering respectively animals, microorganisms other than those used in vaccines, and vaccines." The final correction noted was a typographical error in the word "recombinant" on page 19. He added that with these three very technical revisions that he believed the minutes did an admirable job of capturing the meeting.

Dr. Musgrave said he agreed with the corrections that Dr. Walters had offered and amended his motion to include them. Dr. Walters seconded the motion. Mr. Mitchell called for a vote on the motion, and it was passed unanimously by voice vote.

### III. REPORT FROM THE HUMAN GENE THERAPY SUBCOMMITTEE (tabs 1297, 1298, 1303).

The RAC Human Gene Therapy Subcommittee had met on April 24, 1987. An initial review of a preclinical data document submitted by Dr. French Anderson and colleagues and a document intended to be a layman's guide to human gene therapy were the two items of business which were discussed.

Dr. Walters said that the preclinical document was prepared as a result of an invitation sent by Dr. Gartland to U.S. research groups in 1986 who were known to be working toward gene therapy. The document invited them to test the fit of state-of-the-art laboratory research in this field to the Points to Consider document which had been approved by the RAC.

The document, "Human Gene Therapy: Preclinical Data Document," was coordinated by Dr. French Anderson of the National Heart, Lung, and Blood Institute (NHLBI) together with researchers from the Memorial Sloan-Kettering Cancer Center in New York City who are his collaborators. The document is 86 pages in length and is accompanied with 360 pages of appendices.

Dr. Walters noted that Dr. Anderson and his colleagues raised three central questions as to the current status of laboratory research related to gene therapy:

1. What levels of gene expression in non-human primate models must be achieved in order to offer reasonable hope of benefit to human patients?
2. To what extent must persistence of the added gene be demonstrated to offer a reasonable hope of benefit to human patients?
3. Is a small amount of contamination (at a level of 0.1 percent) with replication-competent virus acceptable in the preparations which will be used to treat the bone marrow cells of patients?

Dr. Walters also said the Anderson Group questioned whether trials with no adverse effects in non-human primates would be sufficient evidence to conclude that such preparations are unlikely to harm human patients.

Dr. Walters said the subcommittee met on April 24, 1987, and discussed these questions with Dr. Anderson, and they decided to circulate the document to outside experts in basic and clinical sciences to gain their insight as to the data reported and issues raised in the document. Further, they decided the comments received from reviewers plus the preclinical data document will become part of a public record which will lead in the future to submission of a clinical gene therapy protocol through the subcommittee to the RAC. The subcommittee set a meeting for December 7, 1987, at which time the reviews and the preclinical document will be discussed as a central topic of the meeting.

Mrs. Witherby then reviewed the draft of a document entitled "Gene Therapy for Human Patients" (tab 1308), which was drafted by six members of the subcommittee to help educate the non-scientific public on the subject of human gene therapy. She said the subcommittee had discussed the document. It suggested that after adoption by the subcommittee, the document be brought before the RAC, circulated for public comment, and eventual RAC approval. Furthermore, she said she was eager to use the document separately for educational purposes.

She said the document is divided into four sections. The first section includes medical facts about genetic diseases, present efforts at treatment, and the possibility of treating a subset of these diseases with somatic cell gene therapy. The second section includes information on oversight and public involvement

along with a history of the subject since the 1970s. The third section summarizes the Points to Consider. Lastly, the fourth section is a listing of materials available for the non-specialist who may be further interested in human gene therapy.

She then asked the RAC members to express their opinions on the document within the next month so that the document can be finalized by the subcommittee at its December 7, 1987, meeting and brought forward to the next RAC meeting.

Mr. Mitchell then called on Dr. Walters for any further comments on the topic of human gene therapy. Dr. Walters said the lay document had attempted to list articles, books, and videotapes which the general public could find useful and understandable. If committee members had any recommendations, the subcommittee would appreciate them.

Dr. Walters said that two members of the subcommittee, Drs. Alexander Capron and James Childress had recently been appointed to the Congressional Biomedical Ethics Advisory Board. One of the first topics the Board will review will be human applications of genetic engineering; and Dr. Walters said the membership overlap between the subcommittee and the Congressional committee will provide for excellent liaison between the RAC and the work of the Congress.

IV: PROPOSAL TO ADD BACILLUS STEAROTHERMOPHILIS TO APPENDIX C-V  
(tabs 1290/II, 1295).

Mr. Mitchell called on Dr. Clewell as primary reviewer. Dr. Clewell said the proposal had come from Drs. Richard Novick and June Polak of the Public Health Research Institute of the City of New York requesting B. stearothermophilis be added to the list of gram-positive bacteria in Appendix C-V of the NIH Guidelines. He noted that recombinant DNA molecules are considered exempt if they are derived entirely from extrachromosomal elements coming from members of the list in Appendix C-V and if they are propagated and maintained in one of the organisms on the list.

Dr. Clewell said the criteria for inclusion on the list is generally a demonstration of inter-species transferability of extrachromosomal DNA, and that exchange of this species with B. subtilis had been demonstrated via transformation. He added that certain plasmids in B. stearothermophilis closely resemble certain other plasmids found in B. sphaericus and Staphylococcus aureus which are already on the list. He concluded that the experimental evidence was sufficient and recommended that the request for inclusion of B. stearothermophilis be approved.

Dr. Davis said he felt the B. stearothermophilis was a particularly valuable organism for research because it is extremely heat-resistant and, therefore, would be of use in obtaining a variety of enzymes. He questioned whether the spelling of the organism was correct in the request and said he believed the ending of the word should be "us" versus "is" as it currently appears. He asked the staff to ensure the proper spelling.

Dr. Gottesman said her only question was whether this organism was explicitly discussed when the original Appendix C-V list was made. Dr. Clewell responded that he felt it was merely an omission or that some information may have been missing at the time which would have allowed it to be included in the original list. Dr. Cohen added that he supported the proposal.

Mr. Mitchell asked if there was anyone present who had any reservations about the proposal to which there was no response. Further, Dr. Gartland stated there were no comments in any correspondence that had been received by the Office of Recombinant DNA Activities (ORDA).

Dr. Davis made a motion that the RAC accept the proposal to add B. stearothermophilis to Appendix C-V of the NIH Guidelines. Dr. Clewell seconded the motion. The motion, having been duly made and seconded, was put to a vote by Mr. Mitchell and was carried by a vote of 18 in favor, none opposed, and no abstentions.

V. PROPOSAL TO AMEND SECTION I-C OF THE GUIDELINES (tabs 1290/I, 1293, 1294, 1301, 1302, 1306, and 1309).

Mr. Mitchell called on Dr. Johnson as primary reviewer to present the proposal. Dr. Johnson said the proposal had been submitted by Mr. Edward Lee Rogers, attorney for the Foundation on Economic Trends, and Mr. Jeremy Rifkin, Foundation on Economic Trends, to add several statements after the first sentence of the third paragraph of Section I-C which, in Dr. Johnson's opinion, was an attempt to define the word "project" in very legalistic terms resembling statutory language which in his opinion was difficult to understand. Furthermore, Dr. Johnson said he felt that since both the NIH Guidelines as well as the RAC were advisory, not regulatory, in nature that the language did not add anything useful to the NIH Guidelines. Also, Dr. Johnson noted that four letters had been received by ORDA, and all four expressed the opinion that RAC should reject the proposal. Among the reasons for the need of such an amendment cited by Messrs. Rifkin and Rogers was the suggestion that the NIH had supported the testing of a Pseudorabies vaccine in Argentina. NIH had concluded that

NIH funds were not expended for the field trial in Argentina. Dr. Johnson recommended the proposed amendment be rejected.

Dr. Korwek said he felt two, rather than one, words were the subject of debate, namely "project" and "supported;" and the Foundation on Economic Trends was attempting to change the interpretation of these words within the context of the NIH Guidelines with the intent of broadening the meaning of these words to preclude any such future tests from lying outside the purview of the NIH Guidelines.

Dr. Korwek said the language of the proposed amendment would accomplish what it had set out to do, i.e., put any possible aspect of any project receiving any sort of funding from the government under the NIH Guidelines; however, he felt the analysis use of National Environmental Policy Act (NEPA) assessment and NEPA applicability could only be ascertained once a project had been shown to fall under the NIH Guidelines.

Further, Dr. Korwek said the proposed language was ambiguous and broad and appeared to include things beyond the scope of the NIH Guidelines, namely "other products and processes of DNA work." He did not know what these were since the NIH Guidelines are limited to recombinant DNA work. In summary, Dr. Korwek said he felt the language was so broad and ambiguous that it would apply to every possible activity; and he felt perhaps this was the goal of the amendment. Further, he questioned the extraterritorial applicability of the NIH Guidelines. He said, however, that if the language were redrafted, he might be willing to support some amendment to clarify the applicability of the NIH Guidelines. He noted that there had been written comments citing the fact that if a reprint was sent to someone and this reprint was used somehow in a project, that under the proposed amendment this would cause the project to come under the jurisdiction of the NIH Guidelines. For these reasons, he said he was opposed to the amendment and recommended against its adoption by the RAC.

Dr. Cohen said he agreed with Drs. Johnson and Korwek. He felt the proposed changes were very broad and vague and that such a change would make the NIH Guidelines all encompassing. He said he understood the Foundation's difficulty with the NIH response on the Argentinean experiment; however, he felt that this was a problem of interpretation that should be taken up with the NIH and did not require a change in the NIH Guidelines.

Dr. Davis said he agreed with Dr. Johnson. He felt it undesirable to make the language of the NIH Guidelines more legalistic and, therefore, more difficult for scientists to deal with. He also questioned the extraterritorial issue. He cited the case of the Sabin live-attenuated polio vaccine which after successful testing in the Soviet Union replaced the Salk vaccine as the regular vaccine for polio immunization in the U.S. He

said that such language, if adopted, would interfere with testing abroad materials that had been discovered in the U.S. and would be undesirable.

Mr. Rifkin was called upon to respond. He said that he was not surprised by the comments he had heard from the committee. He quoted from the NIH Guidelines:

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

Mr. Rifkin said he felt there was a reason for such language and that it was to ensure that projects supported by the NIH would be held up to the same set of standards whether they were carried out in the U.S. or abroad. He used a hypothetical situation to state his case in which an institute was funded by the NIH to test a genetically engineered microorganism and receives millions of dollars of support from NIH for the basic research. The research institute, when it had solved the theoretical problems, decided that it could escape NIH purview by simply funding the end-stage experiment, i.e., release, privately abroad. In essence, the NIH would have paid millions of dollars for the research, but the institute could avoid the purview of the NIH Guidelines by supplying a minor sum of money to fund the final stage. He said, "what you are doing is sending a clear signal across this country and around the world that the guidelines that we adhere to in this country are not the guidelines that we expect other people to have to adhere to in other countries."

Mr. Rogers said the reason he had used the language in the proposed amendment was that he felt the current language in the NIH Guidelines was too general, and he was trying to simply be more precise in his wording. He offered to amend the language to be more in line with the current language. However, he felt the phrase "in kind support" would have to be left for the NIH lawyers to couch in terms which would indicate that what was intended was to avoid the situation in which substantial in kind support is given in lieu of funds but the effect is the same as substantial funding. He said that concerns about reprints and small articles being sent abroad was something that was not intended. He said as far as the term "reasonably foreseeable" was concerned, it has been used in many regulations; and that in NEPA something that is "reasonably foreseeable" is considered within the scope of the project. Furthermore, he said that the word "project" is a word which is currently in the NIH Guidelines and should be clear to everyone. He said the amendment is really an attempt to create a parity between restrictions imposed upon researchers in the U.S., i.e., compliance with the NIH Guidelines, and those who carry out the final stages of their experiments abroad.

Dr. Korwek said he appreciated why the amendment was being brought forward but said that without knowing why NIH interpreted the NIH Guidelines the way they did in the Argentine experiment that it was difficult to know whether such an amendment was justified or not. Dr. Korwek said there were two questions to be asked:

1. In the case of the Pseudorabies vaccine test, was this research funded with NIH funds with only minor private funding for the field test abroad?
2. If all the loopholes are closed, as this proposal is seeking to do, will it not simply force companies and individuals to conduct their research abroad?

Dr. Korwek added that such research will continue to occur and this proposal, "will not be an absolute mechanism to get applicability of the NIH Guidelines." He then asked Dr. Gartland for clarification on the NIH's decision on the Pseudorabies vaccine.

Dr. Gartland said he could not add more than what was stated in letters which are already in the public record and that was the NIH did support research at the Wistar Institute. However, the NIH legal staff took the position that NIH money was not expended in Argentina; and, therefore, the field test was not supported by NIH.

Mr. Mitchell reiterated once again the definition of the words "project" and "support" were unclear and that questions arise: (1) if an experiment is initiated in the U.S., must it be completed here; and (2) if it is initiated with NIH funds and completed abroad, are the NIH Guidelines sufficiently clear to reflect the intent of the RAC?

Dr. Davis interjected that he preferred not to discuss the legal aspects and not to get into the ramifications of such research on U.S. international relations. He added that possibly the State Department should be consulted. He pointed out that Mr. Rifkin had made statements such as, "We don't want to make other countries a dumping ground for our junk." Dr. Davis said he felt other countries had rights. The U.S. is not forcing any country to permit testing. It is an internal decision in those countries to allow such experiments to take place. He said he felt that we should pass no rule which would prevent any country abroad from testing any strains which are produced using recombinant technology which they might find valuable. He asked whether we should set up rules which would restrict a country which may have an epidemic of a disease such as hoof and mouth disease from obtaining a strain of an attenuated vaccine which may solve their problem. He once again cited the Sabin polio vaccine and asked if the same vaccine were newly produced today

using recombinant technology would we feel we had a need to protect the Soviets from their decision to allow testing of the vaccine.

Mr. Rifkin responded by saying it was not a legal point that was being offered but rather whether the RAC considered that the NIH Guidelines should be applicable in other countries when the money that goes into the research comes from this country.

Dr. Rapp said the NIH ruling on the Wistar case isn't something the RAC should be taking up. It may be good to question whether the NIH Guidelines will prevent unexpected deliberate release in other countries with materials manufactured in the U.S. Further, as regards the Sabin vaccine, he said, "if actually Sabin's vaccine had killed a couple of thousand Russian children, would we look at it rather differently?" He said perhaps we had an obligation to ensure that investigators adhere to the NIH Guidelines before sending materials abroad.

Dr. Pirone pointed out that Section I-C as currently written states:

"If the host country, however, has established rules for the conduct of recombinant DNA projects, then a certificate of compliance with those rules may be submitted..."

Dr. Pirone said that if a researcher desired to test something abroad that this could be the way that it could be performed with the consent of the foreign country. Further, he pointed to the sentence in Section I-C which states:

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

Dr. Pirone said he could see how the NIH lawyers could construe portions of a research endeavor to be separate projects. The funding of each project could be construed to apply only to that project and not the overall research endeavor.

Dr. Gartland added that historically the sentence in the NIH Guidelines that states:

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

was inserted in the NIH Guidelines with the intention of covering research grants which were being awarded to foreign institutions.

The word "project" in this sentence has always been construed to be equivalent to "research grant" or "contract."

Dr. Fedoroff suggested two ways of solving the inconsistency between the NIH Guidelines and what other countries find acceptable and that is:

1. Ask whether the NIH Guidelines make sense, given what we now know about recombinant DNA; and
2. What is our current level of experience with recombinant DNA technology.

Dr. Fedoroff said she felt we had enough knowledge base and experience to be able to apply the NIH Guidelines to research abroad as well as in the U.S., and this was reasonable. However, she said she thought changes in the NIH Guidelines lagged behind what is currently known about recombinant DNA and what is going on in research today.

Dr. Gottesman said she wanted the group to get away from the particular wording of the proposed amendment and to consider the issue of the definition of "project," and that the NIH Guidelines as written allow an investigator to follow the rules set up by foreign governments. This addresses one of the major issues. She felt there was difficulty in subdividing a project. She used vaccine development as a case in point and asked if the committee was happy with defining development of the vaccine as one project and the testing of that vaccine as another regardless of where the funding comes from for either phase. She said if the committee was not happy with such an interpretation and development and testing should be considered one project, then perhaps that could be given as advice to the NIH Director without actually changing the NIH Guidelines.

Dr. Epstein said he felt deliberate release of agents developed in this country was the real issue. If the country in which the release takes place has their own guidelines, then they should apply. The problem is in the case of a country that has no guidelines. Perhaps the RAC should consider whether it is necessary to address this issue specifically.

Dr. Davis said testing of a vaccine was merely one of the steps in the overall development of a vaccine and cannot be taken to be a separate project. However, he agreed with Dr. Fedoroff that the NIH Guidelines are slow to evolve. The proposed amendment would impose the NIH Guidelines on other countries possibly to their detriment, and other governments may not react favorably to such restrictions being imposed on them.

Dr. McGarrity took issue with the portion of the proposed

amendment which speaks to "in-kind support" regarding supplies, equipment, use of facilities, and biological research materials. He pointed out that such language could be difficult to supervise and administer in the field of cell cultures. Most of the major cell culture collections are subsidized by the NIH and the Federal government. More than 1,000 cell cultures are shipped overseas each year to a variety of investigators working on numerous projects. If those cell lines eventually were used in recombinant DNA research under the proposed amendment, all of the research, whether it takes place this year, next year, or in 1995, would fall under the NIH Guidelines. He added the same case could be made for bacterial cultures, virus stocks, and animals strains used in research.

Dr. McGarrity asked, "where you have a viable research material, how long does NIH own that if you go by the strict definition of this?" And further, "If I give it to you as an investigator in England and you pass it on to a friend or a colleague and each laboratory propagates that for 5 years, 10 years, is that still NIH-supported material?" He said from both technical and administrative standpoints it would be difficult, if not impossible, to supervise.

Dr. Walters said there were two levels of scrutiny for NIH-funded research, one for the U.S. on an institution-by-institution basis and one abroad on a project-by-project basis. He suggested the possibility of rewriting the first paragraph of Section I-C so that no matter where NIH money is going the institution-by-institution standard would apply. He said this would mean if an institution in India, Japan, or Latin America received any money from NIH for recombinant DNA research, all of their research would fall under the NIH Guidelines; and this would not be reasonable. He said he believed the current standard of project-by-project scrutiny is reasonable for research conducted abroad.

Dr. Johnson said he agreed with Dr. Korwek's comments, and he felt the RAC didn't have the legal right or authority to govern what occurs in another country.

Dr. Joklik said he believed the methods proposed by the amendment were excessive. The amendment's description of "project" would have a, "chilling effect on research, as indeed is substantiated by the letters from responsible people that we've got here." He said he agreed that we did not have the right to impose our NIH Guidelines on foreign governments. He expressed sympathy to the concept but felt the proposal was unworkable.

Dr. Rapp said that despite not wanting to tell other countries what to do, he thought the NIH and RAC could set guidelines for their own investigators regardless of where the investigators carried out their research. He said he believed that in vaccine

development, as the example cited, it was obvious that testing is the aim of the program and it is part of the same research program.

Dr. Cohen said there were three reasons to conduct research abroad rather than in the U.S.: (1) cases in which a disease, condition, or circumstance which you want to test exists in more abundance in another country; (2) to avoid unrealistic delays in the regulatory process; (3) and finally a case in which someone intentionally wishes to avoid adherence to the NIH Guidelines.

Dr. Cohen said he felt the first circumstance can properly be addressed by requiring investigators to get approval of a country's ministry of health by merely a letter stating that the research is in accordance with either their guidelines, their cultural mores, and their concepts as to the rights of individuals. In the second case, unrealistic delays in regulation must be improved and avoided. However, if someone were to attempt to intentionally avoid the NIH Guidelines, then only NIH itself could address this problem, not the RAC.

Dr. Musgrave said he thought the administrative policies of NIH were at the heart of Mr. Rifkin's proposed amendment. Mr. Rifkin believes the NIH should have overall project funding by grants. When in reality, grants are funded in compartmentalized segments in the form of different projects which have clearly delineated administrative beginnings and ends.

Dr. Korwek said the sentence in the first paragraph of Section I-C which reads:

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

is more than administrative. The effect of it, as it stands now, is that the word "projects" is interpreted to mean "research grants." If a new interpretation is needed, then changes would have to be made to the wording of that sentence.

Mr. Rifkin asked the RAC not to table this topic as it had been a long process in getting it to the RAC's attention. He felt it was something of "paramount importance in terms of the interpretation of these Guidelines." Furthermore, he said he would be open to amending his proposal and believed it to be the responsibility of the RAC to help in this effort.

Dr. Pirone offered the following wording to replace the sentence in Section I-C:

"The Guidelines are also applicable to projects done abroad if they are an integral

part of, or a continuation of, research supported by NIH funds."

Mr. Rifkin said that would be suitable.

Mr. Mitchell suggested that the matter be discussed over a break, and perhaps some language could be developed. He then adjourned the committee for its morning break.

Mr. Mitchell reconvened the committee at 10:47 a.m. He said that in all his years on the committee, he did not believe this particular issue and language had ever come up for discussion. Since it was very complex, he would welcome suggestions on how best to continue.

Dr. Pirone said he had an extensive discussion with members of the committee at the break. The consensus was that it could not be resolved at today's meeting. Perhaps a position paper could be assembled, put out for comment, and placed on the agenda for the next meeting of the RAC.

Dr. Walters moved that a working group be set up to study Section I-C of the NIH Guidelines and to report back at the next meeting of the RAC. The motion was seconded by Dr. Pirone.

Dr. Johnson asked that in light of the ruling by NIH counsel whether he would be a part of the working group.

Dr. Joklik supported the setting up of the working group. He restated his views that U.S. researchers not use another country as a "dumping ground" against that country's wish. The other country should have some voice in approving agents for testing within their borders. He believed the language currently stated in Section I-C is sufficient to ensure applicability of the NIH Guidelines abroad when NIH money is involved in the research.

Dr. Korwek said he was in favor of setting up the working group. The Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA) regulations, and other Federal laws need to be looked at in terms of the extraterritorial application of the NIH Guidelines.

Mr. Mitchell asked for further discussion. Upon hearing none, he put the motion to have the Chair appoint a working group to study Section I-C of the NIH Guidelines and to report back to the next meeting of the RAC to a vote. The result of the voting was 17 in favor, 2 opposed, and no abstentions. Mr. Mitchell stated he would announce the committee members at the start of the afternoon session.

Mr. Rifkin asked for a point of clarification as to what would occur should there be a similar incident between today's meeting

and the next meeting of the RAC, and he asked that some appropriate interim policy be established.

Mr. Mitchell replied that it was clear the RAC was taking action and had accepted responsibility for the issue, and the next meeting is scheduled for February 1988. Further, he said he felt it better to take the time to develop a proper position rather than do something which may be regretted.

Dr. Musgrave agreed with Mr. Mitchell and said he didn't think it true that the committee had expressed any feeling that there was currently a problem in the wording of the NIH Guidelines. The only expression of such a problem was made by Mr. Rifkin. He clarified that the experiment which took place in Argentina was not a deliberate release of any organism; it was the testing of an attenuated vaccine, a type of experiment which has been going on for many years. The fact that recombinant technology was used to attenuate the vaccine did not make it any more or less dangerous than any other vaccine ever tested. The mere use of recombinant DNA in a process such as this should not make the process appear dangerous.

VI. PROPOSAL TO AMEND NIH GUIDELINES TO REFER SPECIFICALLY TO RESEARCH WITH PLANTS AND ANIMALS (tabs 1290/III, 1291, 1292, 1300, 1302, 1304, 1305, 1306, and 1307).

Mr. Mitchell called on Dr. McGarrity, Chair of the Working Group on Revision of the Guidelines to present the proposal. Dr. McGarrity said he believed this to be the largest and probably one of the most significant revisions of the NIH Guidelines since 1978. He said the trend had been in general to simplify the NIH Guidelines, to ease containment restrictions, and to place more responsibility at the local level. The proposal being submitted is not an easement, relaxation, or simplification of the NIH Guidelines, but rather an attempt to broaden the scope of the NIH Guidelines. Dr. McGarrity said the present NIH Guidelines deal well with viruses, bacteria, and small animals in the laboratory setting. However, they did not deal as well with large animals and experiments conducted in greenhouses.

As background, Dr. McGarrity said the concept for the proposal had come from the USDA which had expressed a desire to use the NIH Guidelines as a vehicle for oversight of agricultural research involving recombinant DNA. He explained that USDA had held a workshop and developed a draft proposal which was submitted to the NIH and subsequently to the Working Group on Revision of the Guidelines which had met on two separate occasions. Dr. McGarrity thanked Dr. Fedoroff who headed the

subgroup on plant applications, Dr. Gartland, and the ORDA staff for supplying the support necessary to complete the task and bring it before the RAC on short notice. He underlined that this was an excellent example of two Federal agencies working closely together and coming up with something beneficial and productive.

Dr. McGarrity said the proposal as written in tab 1290 appeared to be very confusing and legalistic. He stressed that this was really not the case. Much of the submission in tab 1290 is merely housekeeping to realign paragraph numbering and shift some paragraphs to more closely align them with the sections of the NIH Guidelines to which they refer. He explained that the proposal deals with two sections of the NIH Guidelines, Section II, "Containment," and Section III, "Guidelines for Covered Experiments."

He said the containment section explains the concepts in terms of both physical and biological containment. Most of what the proposal deals with on the animal side is physical containment, while the plant portion of the proposal deals more with the biological containment issues. Dr. McGarrity noted that the problem with the current biosafety levels is that they do not really deal with large animals or plants. The working group developed two new appendices: Appendix P for plants and experiments in greenhouses, and Appendix Q for large animals, which describes biosafety levels for these categories of experiments.

Section III, "Guidelines for Covered Experiments," as currently structured classifies types of experiments into four categories: (1) those that are exempt from the NIH Guidelines, (2) those requiring only notification but not prior approval of local Institutional Biosafety Committees (IBCs), (3) those requiring prior notification and approval of IBCs, and (4) those requiring IBC approval, RAC review, and NIH approval.

Dr. McGarrity said that traditionally in laboratory studies a key item in determining containment levels for an experiment has been Appendix B of the NIH Guidelines, "Classification of Microorganisms on the Basis of Hazard." This classification system has developed from the principle that an organism that has relatively low risk would require BL1 or minimal containment and something with a greater biohazard potential a higher degree of containment: BL2, BL3, or BL4. However, the working group recognized that many organisms used in conjunction with animals and especially with plants had no similar list; and there was no classification system whereby an investigator could readily determine assignment of biosafety levels. He noted that the working group thought such a list should be developed. However, they felt it was not within the scope of their objectives at this point.

Several members of the working group had expressed their desire that someone, either NIH, USDA, or the National Academy of Sciences, should develop such a classification scheme especially for plants. However, the working group did establish a structure for this in order to give investigators some general guidance in the absence of such a classification scheme to be able to establish containment levels on a local level via the IBCs or in collaboration or consultation with others in the field.

Dr. McGarrity said he felt it would be easier for the committee to review the proposal if it were presented in two sections: one relating to the plant sections of the proposal; and one relating to the animal sections. He explained that he would present the animal sections of the proposal, and Dr. Fedoroff would then present the plant sections.

Dr. McGarrity said the containment guidelines for large animals had precedent in and were similar to laboratory practices of the current biosafety levels used for small animals. He said much of the language contained in the proposal was for housekeeping purposes. However, one change that the committee should be aware of was on page 13 of tab 1290, paragraph 35. It is in reference to Section III-B-4-(a) of the NIH Guidelines which currently reads:

"Recombinant DNA, or RNA molecules derived therefrom, from any source except for greater than two-thirds of a eukaryotic viral genome may be transferred to any non-human vertebrate...."

Dr. McGarrity said that everyone recognizes that you could have more than two-thirds of a viral genome without any significant risk. Conversely, you could have far less than two-thirds and create a substantial potential risk. Because of this, the working group simply removed the "two-thirds" terminology so that each experiment could be judged on its own merits.

He explained he did not want to go through Appendix Q in a line-by-line fashion and referred the committee to tab 1307 which summarizes the standard practices, special practices, and facilities required for the different biosafety levels as they apply to large animals. He noted that these biosafety levels have had a suffix added to them to connote the use of large animals; and thus the biosafety levels would be referred to as BL1-N through BL4-N. If an experiment is covered in the laboratory by BL2 and you wished to perform the same experiment in a large animal, you would generally use BL2-N unless the local IBCs had other circumstances they wished to consider.

Dr. McGarrity noted one omission in tab 1307 he wished to bring to the committee's attention. Across the board, the first two lines of every heading should read, "Limited Access" and "Neonate Marking." This would mean that in animals that were transgenic, you would have to have an assayable test for the transgenic sequences. This would be for all containment levels BL1-N through BL4-N.

Dr. Hughes said he would not comment on specific language but only the relevant changes. He said the issue with respect to defining whether a viral vector should be put at higher containment is whether or not the element being used is mobilizable. The intent is to distinguish mobilizable from non-mobilizable elements rather than to set an arbitrary size rule. With respect to classification levels, he said that simple transgenics should be classified BL1-N since there is little possibility of mobilizing the introduced sequences.

He said there was language in the proposal which stated in effect that if you were to try to design your containment facility for a particular experiment, the precise structure of the containment should be such to contain any vector in use. He said there was some language at the end of the proposal which allows for the IBC to lower the classification if a pathogenic strain being worked with can be attenuated in a fashion that is not revertible. This has been added because many of the strains conventionally used as vectors with animals are derived from strains that have considerable pathogenic potential. However, in many cases they are attenuated in such a fashion that makes the classification of the parent strain no longer relevant.

Dr. Richardson said he had particular interest in seeing consistency of proposed amendments to the NIH Guidelines with the publication CDC/NIH Biosafety in Microbiologic and Biomedical Laboratories. He said he had a brief list of some editorial changes and minor inconsistencies as well as some items which he considered major inconsistencies.

Dr. Richardson said he was appreciative of USDA's need to address the issue of large animals which cannot be contained in conventional primary cages. He felt the concept of the entire facility being considered the primary containment, while being logical, created some operational and design problems. He said he would point these out as the discussion continued.

Dr. Gottesman said she had been trying to take the summary of the proposal provided by Dr. Tolin and look at it in relation to the existing NIH Guidelines. She said she agreed that many of the changes were obviously housekeeping, but she was unclear as to how the changes related to the current NIH Guidelines. In relation to the issue of the two-thirds of a viral genome, Dr. Gottesman said she felt this was the most substantive issue

that the proposal had raised. She said the biggest question was whether a class of experiments in animals should be exempted from the NIH Guidelines and if so which class.

Dr. Tolin said the summary provided was simply to guide the discussion and possibly be used by IBCs and investigators as they go through the proposed changes. She said it allows cross-reference on specific paragraph numbers and sections. She said it was not intended to be included in the NIH Guidelines but to be used in aiding the discussion of the proposal and as an appropriate review of containment.

Dr. Korwek said he did not have much to add to what had already been said. However, he had found some inconsistencies as well and felt there was some language that needed to be clarified. He said he felt Dr. Tolin's summary was tremendously helpful. He wished it could be included in the NIH Guidelines, because he thought it had aided him greatly in his understanding of the proposed amendments.

Dr. Epstein asked for clarification on the issue of the two-thirds of a viral genome and asked how the original language had been derived. Further, he wanted to know if it indeed would exempt experiments in Class II.A. which heretofore had not been exempted under the NIH Guidelines as currently constructed.

Dr. Hughes replied to this question by stating that there was an error in the document. The intent had been to classify all injection transgenics as exempt because everyone on the working group felt that if an investigator went to the trouble of making rather expensive large transgenic animals, he would not let them loose in the environment. The logic was that a viral segment that was non-mobilizable was really no different than other DNA and should, therefore, fall into the same classification. He said what was left in the document was remnants of a discussion of whether or not these types of experiments should be exempt or done at the BL1-N level. He said he personally believed they should be exempt, but he did not want to imply that this was the consensus of the working group.

Dr. McGarrity said he had no problem in seeing them done at the BL1 level. The intent was that IBCs would be looking at these experiments.

Dr. Gottesman suggested that if they were to all be at the BL1 level, then the sentence in paragraph 37 could be deleted. However, Dr. Hughes said it may have been placed in the proposal to allow for experiments that will take place at BL1-N and would require notification to IBCs but no review. Dr. Gottesman said her interpretation was that the Section III-B portion of the NIH Guidelines would remain in place, and experiments under Section III-B still require IBC review. None of the animal experiments have yet fallen into Section III-C which would allow for prior

notification with no review required by IBCs. She said she would be concerned about placing these experiments in Section III-C, because it involves a judgment about whether the virus is going to be rescued or be complemented. This should not be left up to the investigator to determine.

Dr. Davis asked whether the current proposed amendment was too complex and whether it should be distributed in this form. Dr. Korwek replied that he had suggested that a document such as the one prepared by Dr. Tolin be promulgated and distributed, and that possibly Dr. Tolin's document could be distributed with the caveat that it is advisory only.

Dr. Davis said he was concerned about having Biosafety Levels 3 and 4 at all for large animals. The issues were twofold: (1) the concern for altered animals, and (2) the concern for microbes on or in those animals. He said that with altered animals and plants there is no need to go to Biosafety Levels 3 and 4. Other regulations already exist to regulate potentially pathogenic microbes. Perhaps some guidelines need to be established for how you handle these microbes when they are on or in large animals and plants.

Dr. McGarrity responded that since the proposal originated from the USDA, perhaps they had conceived of conditions where there would be experiments using Class III or Class IV agents with large laboratory animals, and this had been the assumption that the working group had been working under.

Dr. Davis said he was worried that the public may get the impression that anything involving recombinant DNA, including transgenic animals, might be inherently dangerous.

Dr. McGarrity responded that in Appendix G there already are Biosafety Levels 1 through 4. It is unreasonable to assume that every ongoing experiment is being done at the BL4 level. In fact, the overwhelming majority of experiments are done at the BL1 or BL2 levels, and the same thing will be true of experiments with plants or animals.

Dr. Hughes said the injection transgenic experiments were pulled out of the document at the very beginning and separated just to allay such fears. He stated part of the charge to the working group and the RAC is to provide guidance to the local IBCs to assure people that what is going on is not particularly dangerous.

Dr. Walters said he had a conceptual question in that on page 49 of tab 1290, paragraph 184, where Appendix Q begins it says that this appendix deals with animals or microorganisms associated with animals. He said he wasn't sure how one would know which

microorganisms these were in that the bulk of the document deals with large animals rather than microorganisms associated with them.

Dr. Tolin responded by saying that experiments are assigned two different levels in Appendix Q: (1) the animals at the lower levels; and (2) when microorganisms are added to them, the higher levels are invoked. Dr. Walters asked if it could be rephrased to read, "in terms of microorganisms being tested on animals," because there are many microorganisms associated with an animal that are not intended to be covered, i.e., microorganisms of a cow's digestive tract. Dr. Tolin responded that it really should read, "Recombinant DNA molecules in animals or in microorganisms that are associated with animals," because the intent is that the microorganisms are also modified.

Dr. Musgrave questioned the age limit of 18 in paragraph 285 for unlimited entry into a facility and asked if it paralleled the microorganism guidelines. Dr. Richardson replied that it was an arbitrary age. However, Dr. Tolin noted that it paralleled Appendix G of the NIH Guidelines which is not being changed. Dr. Musgrave asked if the issue was one of informed consent. Dr. Richardson replied that it was more an issue of institutional liability. In most institutions such as the NIH or the Centers for Disease Control where younger students were occasionally employed, it was a general rule that they be excluded from areas of high hazard.

Dr. Musgrave pointed out that through the years there have been many reasons for discrimination in research careers including race, religion, as well as age. He suggested the following phrase be added to paragraph 285 on page 69:

"without written permission of the laboratory director."

Dr. Richardson said it made sense to add such wording. Perhaps originally this wording may have come from the Nuclear Regulatory Commission dealing with radioactive material. Nonetheless, he considered it an arbitrary cut-off.

Dr. Musgrave said that when it came time to make a motion, he would like to have that wording or similar wording added as an amendment to the proposal. Dr. Tolin clarified that currently the NIH Guidelines state that in regard to BL3 containment levels, "Persons under 16 shall not enter the laboratory."

Dr. Davis reiterated that due to the complexity of the document it may have created some misconceptions about recombinant DNA research. He felt the RAC may be going along with this document for the sake of harmony with the USDA. This is not the kind of a document the RAC would have itself written. He said he felt the

concept of just because something is done with recombinant DNA technology does not make it any more or less dangerous than doing the same research through non-recombinant DNA techniques is lost in the complexity of the document. He said he felt a clearer and simpler document was needed to express the RAC's conclusions on these matters.

Dr. Tolin responded that part of the complexity is the form in which the NIH Guidelines are written. The major classifications are based not on biosafety, not on the organism, not on the potential risk of an experiment, but rather on who gives approval and what approvals are required. She disagreed that the RAC should not deal with the issue of large animals and plants. The NIH and other Federal agencies fund research in these areas and other Federal agencies also comply with the NIH Guidelines. Further, Dr. Tolin said that when the USDA attempted to draw up its own set of guidelines, it was told that there should be one set of guidelines for the Federal government. Dr. Tolin said that IBCs have been asking for guidance in these areas. This is an attempt to assure both the public and the IBCs that containment levels are consistent and appropriate for the safe conduct of research.

Dr. Johnson said he agreed with Dr. Davis on the issue of the complexity of the document. He added that he believed the purpose of the NIH Guidelines is not to impede work but to stimulate it. He said he believed this proposal would have the effect of impeding future work.

Dr. Gottesman said she wanted to propose the RAC accept the changes with respect to animals. She believed that the way to proceed was to start moving things into exempt categories or categories requiring less review as a step toward stimulating research.

Mr. Mitchell asked Dr. Gottesman to refer specifically to tab 1290 and the paragraphs if she were making a motion. Dr. Gottesman said the new information which would be added would start on page 11 of tab 1290 and would include paragraphs 17, 21, 25, and 29. All of these refer to simply changing BL1-4 to BL1-N through BL4-N. The next change would be in paragraph 32, changing the title of Section III-B-4 from "Whole Animals and Plants," to "Whole Animals." Paragraph 34, 37, 41, and 182 through 341 would be added as well to the NIH Guidelines. Dr. Gottesman made this in the form of a motion.

Dr. Walters asked Dr. Gottesman to accept as a friendly amendment that the definitional language in the text being moved be duplicated at the beginning of Appendix Q. Dr. Gottesman agreed with the friendly amendment. Dr. Musgrave asked that paragraph 285 be

amended to have the age mentioned therein changed from 18 to 16. Dr. Gottesman accepted this also as a friendly amendment. Dr. Epstein seconded Dr. Gottesman's motion.

Mr. Mitchell asked Dr. Gottesman to clarify the wording of paragraph 37. Dr. Gottesman stated that paragraph 37 would read:

"Recombinant DNA, or RNA molecules derived therefrom, from any source except for a eukaryotic viral genome may be transferred to any non-human vertebrate or any invertebrate organism and propagated under conditions of physical containment comparable to BL1 or BL1-N and appropriate to the organism under study [2]. Animals containing sequences from viral vectors, if the sequences do not lead to transmissible infection either directly or indirectly as a result of complementation or recombination animals may be propagated under conditions of physical containment comparable to BL1 or BL1-N and appropriate to the organism under study...."

Dr. Gottesman said the paragraph then would remain unchanged from the beginning of the next sentence, i.e., "For experiments...."

Dr. Davis asked if this exempted anything new. Dr. Gottesman assured him it did not and it brought everything back to the BL1 level. Dr. Davis asked if there was justification for making it "all transgenic animals." Dr. Gottesman replied that her reading is that transgenics without viral vectors were at the BL1 level as published in the Federal Register. This could possibly exempt some transgenics with a small amount of virus but which were not transmitting it. Dr. Gottesman said she believed it to be more consistent to exempt transgenics in a more orderly fashion. It was not the intent of the working group to look at this issue. In order to do so at this point, it would require justification not addressed in any of the material before the committee. The situation at this point is that no genetic changes in transgenics are exempted, and this proposal will not change that.

Dr. Davis asked if people who are doing research with transgenic animals have been consulted. Dr. Erickson replied that anyone who makes a lot of transgenics currently is doing so at BL1.

Dr. Epstein asked if an exemption could be voted on at this meeting. Mr. Mitchell said it could not. Dr. Epstein said that if such an exemption were desired, it could be brought up at a future meeting. Dr. Davis added that he felt as with bacteria the scientific knowledge base was strong enough to avoid

burdening people with BL1 requirements when dealing with harmless experiments in animals and that such simplifications were desirable.

Dr. Pirone said it may be easier to move for total exemptions at a later date. Dr. Fedoroff pointed out that when the subgroup on plants had started working, they had an objective to exempt as much as possible from the NIH Guidelines. However, the subgroup had decided it was more important to loosen restrictions on what could be done than to exempt things. She said it is not that these experiments should not be exempted, but it would be preferable to take this in two stages.

Mr. Mitchell requested that rather than get into a lengthy discussion on this topic, the committee adjourn for lunch and reconvene in one hour. Whereupon, the committee adjourned for lunch to continue its deliberations at 1:20 p.m. the same day.

Mr. Mitchell called the committee back to order at 1:20 p.m. He noted persons who were interested in purchasing copies of the transcript of today's hearing could place their orders with the official reporter. He also announced that Science had recently devoted a large amount of space to the 100th Anniversary of the National Institutes of Health and informed committee members that there would be a series of events in October 1987 which they may wish to attend.

Mr. Mitchell said some concern had been expressed pertaining to experiments conducted by Dr. Gary Strobel of Montana State University dealing with elm trees, and whether he had violated the NIH Guidelines in these experiments. He noted that Dr. Wyngaarden, Director, NIH, had appointed a committee to look into this matter. He asked Dr. Vidaver if she wished to comment on this matter.

Dr. Vidaver said that she was brought in as an outside consultant to Montana State University. The NIH committee had made recommendations to Dr. Wyngaarden on the experiment in question as to whether Dr. Strobel had a recombinant organism or not. She added that it would be premature to discuss the committee's findings at this point other than to say that the committee had found that the organism in question was not recombinant.

Mr. Mitchell said he had brought this up as an informational item. He assumed the matter was still under review, and he assumed that a report would be forthcoming from the Office of the Director, NIH.

Mr. Mitchell then reminded the committee that a motion was pending on the floor as made by Dr. Gottesman. Dr. Walters then called the question on the motion.

Dr. Gartland asked for clarification as to whether the motion included repeating paragraph 34 at the beginning of paragraph 184 or merely blending this text into 184 in some way.

Dr. Gottesman said she believed it should follow 184. Dr. Epstein said he felt it more appropriate to be inserted after the first sentence of paragraph 184.

Dr. Musgrave asked if Dr. Gottesman had wanted to add anything about requirements for biosafety signs. Dr. Gottesman said she didn't think it was relevant to this discussion. It was an issue possibly pertaining to the plant section of the proposal, and she would discuss it at that time.

Mr. Mitchell repeated the motion to accept paragraphs 17, 21, 25, 29, 32, 34, 37, 41, and 182 through 341, with an amendment to paragraph 285 to reduce the age mentioned therein from 18 to 16. Mr. Mitchell then asked for a vote on Dr. Walters' motion to call the question. The motion to cut off further debate passed by a vote of 19 in favor, none opposed, and no abstentions.

The Chair then called for a vote on Dr. Gottesman's motion. The motion was passed by a vote of 17 in favor, none opposed, and one abstention.

#### VII. RECOGNITION OF RETIRING COMMITTEE MEMBERS.

The Chair noted that there were several members of the committee who were serving at their final meeting. He noted also that Dr. Bernard Talbot, Deputy Director of the National Institute of Allergy and Infectious Diseases had moved to a new position at the NIH. He noted the key role Dr. Talbot had played in the work of the committee dating back to 1975, and he would be sorely missed. He extended both his own appreciation and that of the RAC to Dr. Talbot for his work on behalf of the RAC. A certificate of appreciation would be sent to him. He also presented certificates of service to the RAC to Dr. Rapp, Dr. Pirone, Mrs. Witherby, and Dr. Walters and noted that certificates would be sent to Dr. Sharples and Dr. Bowman.

Dr. Gartland then took the floor to mention that this would be Mr. Mitchell's final meeting as well. He thanked him for his many hours of untiring service to the RAC and to the NIH and presented him with a certificate signed by Dr. Wyngaarden for extraordinary service as Chair of the RAC. Mr. Mitchell responded by saying he had served as an advisor and consultant to many groups, but he felt privileged to have served on the RAC. He said it was, "a unique organization, bringing together so many fine minds and talents on such critical and tough issues." He thanked the group and said he looked forward to having an opportunity to see many of the members again in the future.

VIII. CONTINUATION OF PROPOSAL TO AMEND NIH GUIDELINES TO REFER SPECIFICALLY TO RESEARCH WITH PLANTS AND ANIMALS.

Dr. Fedoroff called the RAC's attention to tab 1291 which was a document she had prepared summarizing the meetings of the sub-group dealing with plants. She said the form of the document was different from that of the NIH Guidelines, and this presented problems to which she and others were sensitive. She said she would present the rationale for the proposal, and Dr. Vidaver would make a presentation on the biological properties of some plant pathogens, the principles of which are key to the containment guidelines proposed.

Dr. Fedoroff said the rationale for the proposal was based on: (1) the recognition that organisms were being dealt with in plant experiments have no recognizable health hazard for either higher animals or humans; (2) the objective of the NIH Guidelines is to minimize the possibility of deleterious effects on organisms and ecosystems outside the experimental facility; and (3) the need to protect the experiment itself from animals and microorganisms from outside the facility.

Dr. Fedoroff noted that not every deleterious effect had been taken into account. Her two major concerns were the spread of a particular pathogenic organism from the greenhouse to a field outside containing plants susceptible to it, and the unintentional establishment of an organism in an ecosystem in which it did not pre-exist and in which it would have detrimental effects on that ecosystem.

Dr. Fedoroff said there was enough experience in both the greenhouse and in the field to justify basing these new NIH Guidelines on standard practices used by plant pathologists and breeders despite the fact that these standard practices are not always consistent. Furthermore, she said a basic principle is that containment appropriate to a recombinant organism should be determined by the biological properties of the original organism and how it was changed not by the technique used to change it.

Dr. Fedoroff said the most important thing in considering the modification of the NIH Guidelines to cover plants, plant-associated animals, and microorganisms is an understanding of how microorganisms associated with plants propagate, become established, or don't become established. She then asked Dr. Vidaver to make her presentation on this topic.

Dr. Vidaver said there were two myths that had surfaced about microorganisms in the environment and associated with plants:

(1) microorganisms don't normally move around, and (2) micro-

organisms readily and easily become associated with plants. Both of these myths were false.

Dr. Vidaver noted that in everyday life microorganisms are readily moved into the sewage system from the microorganisms found on the surface of potatoes simply by peeling them and disposing the peels in the garbage disposal.

She presented a diagrammatic representation of a hexagon to show the many variables of trying to get microorganisms to associate with plants. She explained that this is one of the most difficult experiments to do. It is dependent upon the following: the microorganism itself, the time of the year, the stage of the growth cycle a plant is in, whether the host is even present in the environment, whether a vector is necessary, the environment itself (including temperature and humidity), the presence or absence of water, the presence of other organisms (both micro and macro), pre-emptive microorganisms, and the inoculum load.

Dr. Vidaver presented slides of field plots showing that organisms could be confined on crops in a field environment by a combination of simple biologic and fungicidal procedures. It would prevent any spread of the organism to surrounding plots of the same crop. She then presented slides showing that organisms can be confined to rows of plants within the same field plots. In the greenhouse, she showed pictorial evidence of contained plant viruses on individual plants. She also showed contained pathogenic organisms on single leaves of a plant without infecting other leaves.

Dr. Vidaver said the bottom line was that organisms can be confined if reasonable precautions and care are taken to avoid problems with cross-contamination. Experiments have been taking place for many years with the most potent plant pathogens and even these can be dealt with and confined. She added that since the turn of the century approximately 10 million experiments had been performed with plant pathogens in the field and in greenhouses which is an enormous history on which to base the proposed revisions.

Dr. Fedoroff underlined that the subgroup was working with biological bases. The purpose of the proposal is to give guidance to both the investigator and the IBCs who are seeking guidance on greenhouse containment practices appropriate for use with recombinant DNA experiments involving plants.

Dr. Fedoroff said there were two containment principles which the subgroup established: physical containment and biological containment. Physical containment is normally thought of as being at four levels. In plant experiments, there are only closed boxes and open boxes. She said a closed box is just that, closed. However, a box could be open to differing degrees

by the use of screens or other partial openings. Some of the biological containment practices are genetic manipulations or choices of conditions for the experiment which serve to eliminate or minimize the possibility of biologically meaningful release of experimental organisms. She noted that biological containment practices are in most cases as effective, or more effective, than the physical containment practices.

Dr. Fedoroff said organisms had been divided for administrative purposes: those whose use would require only notification of the IBC, and those requiring prior review and approval. She noted that the classification of these was summarized in tab 1292. Also, the open box containment was appropriate for essentially all experiments involving plants, plant-associated microorganisms, and plant-associated small animals including nematodes. However, "exotic microorganisms" which are defined as those that do not exist in this country and are clearly serious pathogens in their countries of origin would be contained in a closed box.

Dr. Fedoroff said a containment system was set up along the lines of the biosafety levels for microorganisms but that the suffix "P" would be used to connote plants. Therefore, there would be BL1-P, BL2-P, BL3-P, and BL4-P levels of containment.

BL1-P containment would be for experiments in which the plants were non-exotic, innocuous to the ecosystems outside, and where small animals are not involved or can be controlled. BL2-P would have screens added over the windows to protect not only the outside from the inside but also the inside from the outside and is relevant when insect vectors are involved. BL3-P and BL4-P are both closed boxes with the difference being in the stringency of filtration of what goes in and out of the facility and how well it is isolated from the surrounding area. Dr. Fedoroff noted that she was unclear as to whether the BL4-P was necessary for any organism but that a short list of organisms requiring this level of containment does exist.

As far as biological containment principles, Dr. Fedoroff noted that these were different procedures to limit dissemination of plants, the microorganisms associated with them, and the small animals associated with them. There are some simple procedures such as covering reproductive structures and collecting seeds, using male sterile plants, or ensuring no plants that can cross-fertilize are within the distance that pollen can disperse. Other procedures may include working with a serious plant pathogen that is extremely contagious and associated with a plant in the winter. Microorganisms can be injected and attenuated strains can be used. A very important biological control is carrying out experiments in the absence of any vector required for transmission. Another choice could be to use microorganisms that have an obligate association with the plant.

Furthermore, microorganisms that are genetically disabled to minimize survival outside the test facility or whose natural mode of transmission requires injury of the target organism in some other way, may allow an investigator to reassure an IBC that inadvertent release is unlikely to initiate and propagate infection of organisms outside the experimental facility.

For macroorganisms, either non-motile or sterile strains could be used or the experiment could be conducted in the winter. In the case of nematodes, water collection could be used. Screens or cages could also be employed.

Dr. Fedoroff said that at this point she would like to open up the topic for discussion and asked for comments.

Dr. Korwek asked what exactly was a "noxious weed," because he believed there was to be a reference included for such terminology. Dr. Fedoroff said that it was cited in the original document, but perhaps this reference may have been omitted. She said she would ensure that it be included in the final proposal.

Dr. Walters said that tab 1290, paragraph 70, showed only Biosafety Levels 1 through 3 and questioned whether there should be a fourth. Dr. Tolin agreed. Dr. Fedoroff noted that this was a typo and needed to be changed to reflect Biosafety Levels 1 through 4.

Dr. Fedoroff noted that one of the major comments is that it would be unnecessary to put up biohazard signs when all the evidence was that these experiments were perfectly safe. She said in the original document the suggestion had been to only put up biohazard signs if certified pathogens were involved in the experiments. This has even been questioned in the public responses to the Federal Register notice. Dr. Fedoroff said that traditionally any experiment involving recombinant DNA had a requirement for the biohazard sign to be in place. Also, the subgroup had felt there was no need for a requirement for non-exotic pathogens and for any experiment done in an open box.

Dr. Richardson said the biosafety guidelines were written specifically for host-specific animal pathogens and zoonotic agents. The biohazard warning sign was to serve as an alert as far as human risk. Therefore, there is no requirement for a warning sign at Biosafety Level 1. At Biosafety Level 2, the biohazard warning sign indicates special conditions for entry into the laboratory. If those were not applicable in the case of either Appendix Q or Appendix P, there would be no reason to require a biohazard sign. However, at Biosafety Levels 3 and 4 the sign would become universal at all points of entry.

Dr. Fedoroff asked Dr. Gartland for guidance as to how this could be handled and whether it was necessary to incorporate such statements as part of a motion when a motion is made to either approve or disapprove the proposed NIH Guidelines. Dr. Gartland said he believed the process used in the morning session in discussing animals would be a proper one to be followed in this case. Dr. Fedoroff then said she would add notations that biohazard signs are only required at BL3-P and BL4-P in any motion that would ensue.

Dr. Davis asked why there was a concern about introducing potent vertebrate toxins into plants. Dr. Fedoroff replied that there would really be little concern with such an experiment unless it could spread by normal genetic means to food crops. Further, if there was a biological control in place such as doing the experiment in the wintertime, there was no need to use a closed box to perform such an experiment.

Dr. Pramer said the subgroup had sought ways of containing plants, and associated microbes, and insects in order to minimize possible detrimental effects to organisms or ecosystems outside the facility. It was done with sufficient breadth and flexibility to assure that research could be conducted and conducted safely. The proposal is effective in this regard.

Dr. Fedoroff said she wanted to address some specific issues that had been brought up in correspondence relating to the proposed amendments to the NIH Guidelines. She said one of the statements made is:

"Because the Guidelines apply to a very wide range of organisms and experimental designs, not every circumstance can be anticipated and a thoughtful evaluation must be made of the biological and ecological properties of the organisms involved in a given experiment."

She said this applies as much to selecting more stringent conditions as relaxing them where necessary. Each experiment must be looked at to ensure correct categorization of biosafety levels required based upon the local geographic area, the season, possible vectors of transmission, et cetera.

Dr. Fedoroff noted that there was a suggestion that the term "insect" be replaced by the term "Arthropod" throughout the document, and she felt this was perfectly reasonable. Dr. Walters asked for clarification of this. Dr. Richardson explained that all insects are Arthropods, but not all Arthropods are insects. "Arthropod" is a more appropriate term for the group of organisms which may be involved in physical transmission. Dr. Pirone added that it would also include mites, which are arachnids rather than insects.

Dr. Gottesman said she felt it would be good to go through the same type of exercise with the plants as was done with the animals. This is to analyze what is actually being done by the proposal in relation to what currently exists in the NIH Guidelines. She said her interpretation was that since pathogens for plants are not normally pathogens for humans or animals, essentially anything with whole plants, if less than two-thirds of the eukaryotic viral genome were being introduced was to be performed at BL1. The rest would require review and approval by the IBC and would fall under the Section III-B category of the NIH Guidelines.

Dr. Fedoroff said that was her interpretation, but there was no provision in the NIH Guidelines for working in an open greenhouse. Dr. Gottesman said the issue was really that a greenhouse was not defined in the original NIH Guidelines. Appendix P, paragraphs 72 through 161, provides a description of greenhouses, how to work with them, and what practices are appropriate. This would be new information.

Dr. Gottesman said there were three things that had been done essentially. Paragraph 68 states that whole plants regenerated from cells in tissue culture, but still in axenic cultures, should remain exempt. If tissue culture is exempt, what would happen if a plantlet were regenerated from it? It previously was exempt in tissue culture. Dr. Tolin said this was merely a clarification, and it is just differentiated tissue.

Dr. Gottesman said that a hierarchy of risk had been set up to place experiments in the Sections III-B and III-C categories of the NIH Guidelines requiring IBC notification and review and approval, and this was a change in the NIH Guidelines. Dr. Fedoroff said this would also act to give guidance to IBCs, and would clarify that experiments with exotic pathogens would require prior approval by the IBCs. Also, it allowed IBCs to reclassify experiments for containment requirements based on biological controls that are inherent on an experiment-by-experiment basis.

Dr. Gottesman said she felt uncomfortable that some experiments could be performed at a given containment level without first being approved by the IBC but merely by notifying the IBC that the experiment was being done at that level. In the past with animal pathogens, approval of containment must first be looked at by the IBC. Dr. Tolin replied that currently with any experiment where only notification of the IBC is required that the IBC is still responsible to review the proposals. This can be done after initiation of the experiment. Based upon the biology and prior experience, the experiment could be stopped and containment raised.

Dr. Gottesman asked for clarification of the term "potent" in paragraph 48a of tab 1290 and asked whether this was meant to be a change from existing NIH Guidelines. Dr. Fedoroff replied that the only changes made to the paragraph were to insert specification of greenhouse conditions for plants containing genes for potent vertebrate toxins. Dr. Gottesman said the use of the word "potent" was still unclear and could provide problems in the future. Dr. Fedoroff asked Dr. Gartland to clarify the wording to reflect the conclusions of the plant subgroup. Dr. Gartland said that a cross-reference could be added to Section III-A-1 of the NIH Guidelines.

Dr. Davis said he had suggestions for page 7, paragraph 4, of tab 1290. He said just because something can spread does not assume that any harm will take place. He offered the following substitute wording for the second sentence of paragraph 4:

"Biosafety Level 1 for plants (BL1-P) is designed to provide a moderate level of containment for specific recombinant DNA research involving plants and is recommended for experiments for which there is convincing biological evidence that precludes the possibility of survival, transfer, or dissemination of the recombinant DNA molecules into the environment, or for which there is no recognizable and predictable risk to the environment in the event of accidental release."

Dr. Fedoroff said this would be appropriate.

Dr. Davis said he also had a suggestion to clarify and change paragraph 5 on page 8 of tab 1290. The second sentence uses the word "minimizes." This would denote using maximum levels of containment for all experiments. He suggested the second sentence be amended to read:

"Such facilities and procedures, through providing a modified and protected environment for propagation of plants and of microorganisms associated with the plants, also provide a degree of containment that adequately controls the potential for release of biologically viable plants, plant parts, and microorganisms associated with them."

Dr. Fedoroff agreed the substitution would enhance the meaning of the sentence and be what the subgroup had intended.

Dr. Pirone said he thought paragraph 88 on page 26 contained some inconsistencies referring to the BL1-P practices. The sentence in question was:

"It should advise personnel of potential consequences if practices are not followed and outline contingency plans in the event containment loss results in release of organisms with recognized potential for serious detrimental impact."

Dr. Pirone said if there was recognized potential for serious detrimental impact perhaps BL1-P was not the proper containment. Therefore, the final portion of the sentence should be deleted following the word "followed" making it read:

"It should advise personnel of potential consequences if practices are not followed."

Dr. Fedoroff said she agreed with the change, and Dr. Tolin concurred.

Dr. Pirone said paragraph 98 of tab 1290 had the same wording, "serious detrimental impact." Perhaps this sentence should be made to read:

"It should advise personnel of potential consequences if practices are not followed and outline contingency plans in the event containment loss results in release of organisms."

Dr. McGarrity said it may be better to be consistent with the language in paragraph 88 and end the sentence after the word "followed." Dr. Pirone said in light of the fact that the containment level here was higher and at a minimum there would be screens on the greenhouse, it should contain the wording up to the word "organisms." Dr. Fedoroff agreed with this.

A third inconsistency was pointed out by Dr. Pirone in paragraph 103a dealing with the same wording, "serious detrimental impact." Dr. Fedoroff said that 103a was going to be totally eliminated, and there would be no need to consider amending its text.

Dr. Fedoroff said that there had been a similar suggestion made by the Industrial Biotechnology Association (IBA) in reference to paragraph 89. They recommended it to read:

"A record is kept of experiments in progress in the facility."

Dr. Fedoroff said the IBA pointed out that many times investigators will need to remove soil samples and plant parts from a greenhouse to a laboratory for characterization. Maintaining a log would be burdensome and would be inconsistent with the risk of experiments at that containment level. She suggested the IBA language be substituted for paragraph 89 as printed in tab 1290. Dr. Tolin underlined that this would only be for experiments at BL1-P.

Dr. Pirone said he also had found Dr. Tolin's summary an excellent aid to understanding the proposed changes in the NIH Guidelines. He suggested it be made available through some mechanism to the IBCs.

Dr. Pirone said he was also confused about possible exceptions for some experiments which may be judged to be at the BL3-P containment level. When evidence of biological containment exists, it could be as safely performed at the BL2-P level. He said he felt this rationale should be more "up front" and suggested that paragraph 44 be deleted in its entirety, and the following wording be added to paragraph 46:

"BL3-P or BL2 plus BC containment is recommended...."

Dr. Gottesman said she thought paragraph 44 was still useful to have in the document. Dr. Pirone agreed saying the suggested wording could be added to both paragraphs 44 and 46; but he wanted it in paragraph 46. He felt this would be more consistent and put the issue up front for both the investigators and the IBCs. Dr. Tolin said she thought this was the intent of the working group.

Dr. Richardson pointed out an inconsistency with paragraphs 108 and 114. Paragraph 108 offers no alternative to autoclaving plant materials at BL2-P, whereas paragraph 114 provides alternatives to autoclaving. Dr. Fedoroff asked Dr. Gartland to assure that these two were consistent.

Dr. Richardson asked if there was scientific justification for high efficiency particulate air (HEPA) filtration of exhaust air from the BL3-P facility as is required in paragraph 133a. Furthermore, in paragraph 160, there were provisions which required a back-up source of power, meaning an emergency generator, at BL4-P which would exceed requirements for maximum containment laboratories working with such hazardous materials as Lassa fever virus.

Dr. Fedoroff said she felt the whole category of BL4-P was unnecessary. She felt the requirement for a back-up power source could and should be eliminated. She added that the requirement for an autoclave was something that had come up in

the original version of the document and should have been stricken in the final version. Dr. Fedoroff said that the IBA letter had also contained some suggestions on changing the wording of the second sentence of paragraph 100 to read:

"Decontamination of run-off water is not necessarily required."

She said she agreed with this and proposed the language be changed to reflect this. Also, the IBA proposed doing away with paragraph 91c in its entirety which relates to biological signs for BL1-P containment. Dr. Fedoroff and Dr. Tolin agreed that this was an acceptable amendment to the proposal.

Dr. Vidaver said she had an addition to paragraph 106a. She suggested a sentence be added to say that, "Soil beds are also acceptable unless propagules of experimental organisms are readily disseminated through soil." She said there could be some question about doing such an experiment with the current wording of 106a. As long as they remained confined, she saw no reason not to have soil beds inside greenhouses. She also said it had been suggested that in paragraph 50 the beginning of the second sentence be changed from the wording, "Recognition as to whether..." to "Determination of whether or not...." Dr. Fedoroff agreed with both changes.

Dr. Walters asked regarding the last sentence in paragraph 88 on page 26 whether the "potential consequences" referred to were ecological consequences or administrative consequences. After discussion, it was determined to remove the entire last sentence from paragraph 88.

Dr. Korwek said that there were still some inconsistencies in paragraphs 100 and 114 referring to the use of autoclaves for sterilization. Dr. Tolin replied that at BL1-P organisms could be killed by means other than autoclaving; and it leaves it to the investigator to determine the best method for inactivating organisms. Dr. Korwek said in that case the terminology "rendering biologically inactive" was redundant. Dr. Pirone said he felt it was clear without the use of the word "autoclave" that any means to biologically inactivate an organism was all that was needed.

Dr. Fedoroff said the original document before translation into the language of the NIH Guidelines simply said:

"Experimental organisms are rendered biologically inactive by appropriate method before disposal."

She asked Dr. Gartland to reword this in paragraphs 100 and 114 to ensure the original intent was clear.

Dr. Morris Levin of the Environmental Protection Agency said he felt the proposal was well thought out and constructive. He felt the references to doing experiments in the winter should be clarified as to what was meant by "winter" and whether a mild winter would have an effect on such experimentation. Dr. Pirone answered that in most cases host plants for pathogens are killed by the first frost. Therefore, a mild winter would still permit such experiments to continue. He added that if the host were a weed perhaps this could be a problem, but he emphasized that once again knowledge of the biology of the organisms involved is what is important. Good judgment on the part of investigators is paramount.

Dr. Fedoroff replied that the responsibility is on the principal investigator to make sure he knows the biology and is able to defend it to his IBC. It is the responsibility of the IBC to evaluate the case presented to it by the investigator.

Dr. Henry Miller from FDA said that most of the FDA suggestions had been incorporated, but he had two further suggestions. He said that in paragraph 133a there was a statement that for BL3-P, "Air supply filters shall be 80-85% average efficiency by the American Society of Heating, Refrigerating, and Air Conditioning, Inc. (ASHRAE) standards...." He said he was unfamiliar with ASHRAE standards and suggested that it should say, "better than 80% efficiency," instead of specifying further parameters. Dr. Richardson replied by saying there is no air supply standard in the biosafety guidelines currently in place. Therefore, the standard for supply air in this proposal exceeds that of the parent document.

Dr. Miller questioned why, in paragraph 101, nematodes and flying insects were referred to as "microorganisms." Dr. Fedoroff replied that apparently it was a typographical error and should read "macroorganisms."

Dr. John Payne from USDA said there were some changes regarding footnotes referring to USDA regulations; in particular, changes to footnote 18 which he would supply to Dr. Gartland for inclusion in the final proposal.

Dr. Vidaver then moved that, "RAC accept the modifications along with the language in Appendix P plus the pertinent paragraphs in the sections dealing with plants that we have just discussed and that these be incorporated into the Guidelines." Dr. Pirone seconded the motion.

Dr. Walters moved to close debate and his motion was seconded by Dr. Korwek. The Chair put the motion to close debate to a vote, and it passed by a vote of 14 in favor, none opposing, and 2 abstentions.

The Chair then asked for a vote on the main motion. The result of the vote was 14 in favor, none opposing, and two abstentions.

Dr. Gottesman noted that paragraphs 6, 7, 8, and 9 in the containment section of the proposal dealing with animals had been inadvertently left out of her previous motion. Mr. Mitchell asked if there was objection to these paragraphs being added to the motion. There was no objection voiced by the committee.

Dr. Miller said that there may be an oversight in the proposed Appendix Q. He said that paragraph 196 contained a requirement for marker sequences in transgenic animals. The current state-of-the-art did not guarantee that such sequences would be used in all experiments. The phrase "where practicable" should be inserted in paragraphs 196, 206, 236, and 278, in order to avoid an absolute requirement for marker sequences. Dr. Erickson disagreed and replied that in every case of a transgenic animal the inserted gene in effect becomes the marker gene.

Dr. Tolin pointed out that paragraphs 52, 53, and 70 of the proposal had not been included in any motion and contained language necessary to make the other proposed changes consistent with the NIH Guidelines. The Chair asked if there was objection to the inclusion of these paragraphs in Dr. Vidaver's motion; and in hearing none, the motion was amended to include those paragraphs.

Dr. Musgrave said he had abstained because of the multitude of changes to the proposal. He asked if possibly the changes that were discussed could be incorporated in a document by Dr. Gartland and brought back to the committee to ensure that it was the sense of the committee. The Chair said the committee had seemed substantially aware of the sense of all the changes. If there were any questions, the members of the working group would be consulted by Dr. Gartland. Dr. Gartland confirmed that if there were any questions as to the final wording that he would refer these matters back to the Working Group.

Dr. Walters noted that RAC members are only temporarily on the committee, but Dr. Gartland and his staff had provided excellent support to the committee over the years. He formally thanked Dr. Gartland and his staff for their excellent support.

#### IX. FUTURE MEETING DATES (tab 1296).

Mr. Mitchell announced that the next three meetings would be February 1, June 3, and September 30, 1988. Dr. Gartland said that the September 30 meeting date had been changed to Monday, October 3, 1988.

Having concluded the agenda and there being no further business to be discussed, Mr. Mitchell adjourned the committee at 3:37 p.m. on September 21, 1987.

---

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

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

Date: \_\_\_\_\_

---

Robert E. Mitchell, LL.B.  
Chairman  
Recombinant DNA Advisory Committee  
National Institutes of Health