

978

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

RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING¹

SEPTEMBER 25-26, 1980

The Recombinant DNA Advisory Committee (RAC) was convened for its twentieth meeting at 9 a.m. on September 25, 1980, in the Linden Room, Linden Hill Hotel, 5400 Pooks Hill Road, Bethesda, Maryland 20014. Mr. Ray Thornton (Chairman) President, Arkansas State University, presided. In accordance with Public Law 92-463 the meeting was open to the public, except for the review of proposals involving proprietary information as the last item of business on September 26, 1980.

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

Dr. Abdul Karim Ahmed; Dr. Kenneth Berns; Dr. Winston Brill; Dr. Allan Campbell; Mrs. Zelma Cason; Dr. Nina Fedoroff; Dr. Richard Goldstein; Dr. Susan Gottesman; Dr. Jean Harris; Ms. Patricia King; Dr. Sheldon Krinsky; Dr. Werner Maas; Dr. James Mason; Dr. Gerard McGarrity; Dr. Elena Nightingale; Dr. Richard Novick; Dr. Ramon Pinon; Dr. John Scandalios; Dr. Luther Williams; and Dr. William J. Gartland, Jr., Executive Secretary.

A Committee roster is attached. (Attachment I)

The following ad hoc consultants to the Committee were present:

Dr. Vee J. Gill, Clinical Center, NIH; Dr. Vernon Knight, Texas Medical Center, Houston, Texas.

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

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

Dr. Daryll Banks, Environmental Protection Agency; Dr. Charlotte Bell, U. S. Department of Justice; Dr. Donald DeVincenzi, National Aeronautics and Space Administration; Dr. George Duda, U. S. Department of Energy; Dr. Timothy J. Henry, Food and Drug Administration; Dr. Herman Lewis, National Science Foundation; Dr. David Logan, U. S. Department of Labor; Dr. Sue Tolin, U. S. Department of Agriculture; and Dr. William J. Walsh, III, U. S. Department of State.

Other National Institutes of Health staff present were:

Dr. Marilyn Bach, NIAID; Dr. Stanley Barban, NIAID; Dr. W. Emmett Barkley, ORS; Mrs. Betty Butler, NIAID; Dr. John Irwin, ORS; Dr. Richard Krause, NIAID; Ms. Chris Krutzsch, NIAID; Dr. Robert McKinney, ORS; Dr. Elizabeth Milewski, NIAID; Dr. Stanley Nagle, NIAID; Dr. John Nutter, NIAID; Dr. Maxine Singer, NCI; Dr. Bernard Talbot, OD; Dr. Rudolf Wanner, ORS; and Dr. Burke Zimmerman, OD.

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

Dr. Lucile Adamson, Occupational Safety and Health Administration; Dr. E. A. Agostini, Pfizer, Inc.; Dr. D. E. Baldwin, Schering Corp.; Dr. Howard Bermann, U. S. Veterans Administration; Ms. Irene Brandt, Eli Lilly & Co.; Dr. Peter Bostock, New Brunswick Scientific Co.; Inc.; Ms. Vicky Cahan, McGraw Hill; Dr. C. T. Chen, Occupational Safety and Health Administration; Mr. Jeffrey Christy, Blue Sheet; Mr. Chris Coley, Harvard Medical School student; Dr. Aileen Compton, Smith-Kline & French; Mr. David Dickson, Nature; Dr. Diana Dutton, Stanford University; Dr. John Grupenhoff, Washington Counsel/Medicine and Health; Dr. Lowell Harmison, Office of Assistant Secretary for Health; Dr. Zsolt Harsanyi, Office of Technology Assessment; Ms. Flo Hassell, Office of Assistant Secretary for Health; Mr. Phil Hilts, Washington Post; Dr. Paul Hung, Abbott Research Laboratories; Dr. James Hunt, Chemapec; Dr. Evelyn Hurlburt, Johns Hopkins School of Hygiene; Mr. Philip Janus, Office of Assistant Secretary for Health; Dr. Dorothy Jessup, U. S. Department of Agriculture; Dr. Irving Johnson, Eli Lilly & Co.; Dr. Attila I. Kadar, Food and Drug Administration; Mr. B. Khosrovi, Cetus Corp.; Mr. Edward Korwek, Kells & Heckman; Ms. Ann Lallande, McGraw Hill; Dr. Paul Leibowitz, Schering Corp.; Ms. Carter Leonard, Blue Sheet; Dr. M. A. Levin, Environmental Protection Agency; Dr. James McCullough, Library of Congress; Dr. Henry I. Miller, Food and Drug Administration; Mr. Claude Nash, Smith-Kline & French; Dr. DeLill Nasser, National Science Foundation; Dr. Ann Norberg, Monsanto Co.; Dr. Arthur Norberg, National Science Foundation; Mr. Seth Pauker, National Institute for Occupational Safety and Health; Dr. William Pilacinski, Molecular Genetics, Inc.; Mr. Alvin Polan, SELF; Dr. John Richardson, Centers for Disease Control; Mr. Harold Schmeck, New York Times; Dr. Brian Sheehan, Consultant, Amos Corp.; Mr. Vincent Simmons, Genex Corp.; Dr. Mark Smith, CNAM, Paris; Mr. Jeff Swarz, Teknekron, Inc.; Mr. Dean Taylor, Smith-Kline & French; Dr. Charles Weiner, Massachusetts Institute of Technology; Dr. Marvin Weinstein, Schering Corp.; Dr. Susan Wright, University of Michigan; Dr. Bill Young, Genentech, Inc.; and Dr. Robert Zaugg, Teknekron, Inc.

I. CALL TO ORDER AND OPENING REMARKS

Mr. Thornton introduced a new RAC member, Dr. Nina Fedoroff of the Carnegie Institution of Washington, and Dr. Vernon Knight of Baylor College of Medicine, Texas Medical Center, an ad hoc consultant.

II. MINUTES OF THE JUNE 5-6, 1980 MEETING

Ms. Cason said she found the draft minutes (tab 939) of the June 5-6, 1980 RAC meeting to be complete with no substantive errors. Ms. Cason moved approval of the minutes with suggested corrections of typographical errors. The minutes were unanimously accepted.

III. SURVEY OF INSTITUTIONAL BIOSAFETY COMMITTEES IN CALIFORNIA

Mr. Thornton invited Dr. Diana Dutton of Health Services Research, Stanford University School of Medicine, Stanford, California to present the results (tab 937) of the survey of California Institutional Biosafety Committees (IBCs). Dr. Dutton said a group at Stanford University began about two years ago to study the process of policy making in biomedical innovation, particularly the public's role in the process. The group viewed the mandating of IBC composition by the 1978 National Institutes of Health (NIH) Guidelines as an experiment in local public participation in science regulation. She emphasized that the findings she would present to the RAC were suggestive but not definitive.

Dr. Dutton said the survey consisted of a questionnaire sent to all IBC chairpersons in California, and a separate questionnaire sent to all nonaffiliated members of California IBCs. Ninety-five percent of all

IBC chairpersons responded (19 responses out of 20 surveyed) as did ninety-two percent of all non-affiliated members contacted (45 out of 49). Some of the findings were summarized in a document which Dr. Dutton distributed at the meeting (Attachment II).

The average IBC is composed of eleven members. The majority of committee members are scientists: twenty-eight percent are "recombinant DNA scientists," and twenty-seven percent are "other life scientists." Public health officials constitute twelve percent of the typical committee. Other categories of membership include students, laboratory workers, local citizens, etc.

The majority of IBC chairpersons (56%) indicated that the IBC had no relationship to local government. The average number of meetings held in 1979 was 4.3. On the average, sixty-three percent of the meetings were not regularly scheduled. Four of the nineteen committee chairpersons indicated that some meetings were held by telephone or in writing. The agenda of the typical meeting was roughly divided equally between review of MUAs and discussion of policy matters and other business. The committees on the average reviewed sixteen MUAs in 1979, but the range went from one MUA to sixty-eight MUAs. The amount of time spent in review of an MUA averaged thirty-two minutes, but values ranged from six minutes per MUA to an hour and forty-three minutes per MUA. Four percent of all MUAs were rejected. Dr. Maas pointed out that draft MUAs are often first checked informally with the IBC Chairman or with ORDA before formal submission to the IBC.

Less than a third of the committees felt that special health surveillance was necessary in regard to emergency plans in case of accidental spills. Some IBCs focused on internal laboratory procedure, others focused on the relationship between laboratories and external agencies. The task of training laboratory staff was delegated primarily to the principal investigator. Training for IBC members ranged from none to a fairly elaborate system involving training documents, discussions and laboratory tours.

The assessment of the Guidelines and IBC function by the chairpersons and the nonaffiliated members was, on the whole, positive. The chairpersons tended to emphasize the positive aspects of Guideline flexibility, while the nonaffiliated members stressed the watchdog and public relations role of the IBCs.

While the majority of non-affiliated members are local citizens or public health officials, some twenty-five percent are life or recombinant DNA scientists. Dr. Dutton felt that latter is not in technical violation of the Guidelines but is in some conflict with the intent of the Guidelines. Both the chairpersons and the nonaffiliated members were modestly positive about the role of nonaffiliated members. Sixty-one percent of the chairpersons felt the stipulation that twenty percent of the IBC membership be nonaffiliated was appropriate. Thirteen percent of nonaffiliated members thought their contribution was not valuable. Approximately half of the committees said all their meetings were open to the public; about half said none of their meetings were open to the public. Dr. Dutton felt IBCs

were not making sufficient effort to reach out into the community and solicit participation. In conclusion, Dr. Dutton noted great diversity in California's IBCs with respect to their membership, scope of activities, performance, etc.

The Committee discussed with Dr. Dutton her data and her interpretation of them. Dr. McGarrity questioned whether unannounced meetings could be termed open public meetings. Dr. Berns said that advertising a meeting far in advance introduced an element of inflexibility into scheduling.

Dr. Ahmed asked Dr. Dutton to state her conclusions on industrial IBCs. Dr. Dutton replied that industrial IBCs compared to university IBCs are less accessible to the public, have higher MUA approval rates, have more elaborate health surveillance programs, and provide better training for staff and IBC members.

IV. MEETING OF INSTITUTIONAL BIOSAFETY COMMITTEE (IBC) CHAIRPERSONS AND IBC SURVEY

Dr. Krause, the Director of the National Institute of Allergy and Infectious Diseases (NIAID), said that the NIH sponsored an IBC chairperson meeting approximately two years ago. He said NIAID now would sponsor a second IBC chairperson meeting on November 24-25, 1980. Dr. Krinsky and several IBC Chairmen are on the Planning Committee. Dr. Nutter said the November 1980 meeting would serve two purposes: (1) it will permit IBC chairpersons to meet and attempt to resolve common problems, and (2) it is viewed as the first stage in a formal evaluation process. He invited RAC members to

attend. He then reviewed the format of the meeting; a plenary introductory session the first morning, will be followed by three separate workshops that afternoon. The workshops deal with (1) the IBC as a means of implementing institutional oversight, (2) health surveillance, monitoring and certification, and (3) procedures and operations. A second plenary session during which workshop teams will report is planned for the second morning. This session will be followed by a plenary session dealing with other federal regulations and guidelines impacting on biomedical science.

Dr. Nutter noted that a Request for Proposals (RFP) is being developed to evaluate all IBCs. Based on the results of the November 24-25 meeting, the RFP may be reviewed. Dr. Gottesman noted that Dr. Dutton's survey evaluated public participation in IBC operation. She said a second important question is the effectiveness of the IBC in assuring compliance with the containment levels of the Guidelines.

V. PROPOSED PROCEDURES FOR REVIEW OF LARGE-SCALE APPLICATIONS

Dr. Logan of OSHA distributed copies of a September 24, 1980 letter from Dr. Bingham to Dr. Fredrickson (Attachment III). Dr. Gottesman reviewed the background of the proposal for revised procedures for review of large-scale applications. She noted that at the past few RAC meetings, there has been extensive discussion of the role of RAC and of the NIH in the review of large-scale proposals particularly submitted by industrial concerns. She moved approval of the following proposal which had been published in the Federal Register (tab 931/7) of August 21, 1980 for comment:

"The following procedures should be adopted for approval of requests to grow greater than 10 liters of organisms containing recombinant DNA. The RAC will determine if a given recombinant DNA-containing strain is rigorously characterized and the absence of harmful sequences established. Such a determination shall include specification of a containment level (P-LS). These determinations should not in any way be construed as RAC certification of safe laboratory procedures for industrial scale-up. Adherence to the specified containment conditions is the responsibility of the local IBC."

Following this proposal, there appear in the Federal Register of August 21, 1980, proposed revised application procedures to implement this change. Dr. Gottesman said under this proposal the IBC would accept responsibility for assuring adherence to the physical containment guidelines. She said RAC would continue to evaluate the biology of the recombinant clones and the host-vector systems, but no longer deal with prereview of physical containment in individual applications.

Dr. Krinsky said he had supported this proposal at the June 1980 RAC meeting. He had felt then that a government agency, such as the Occupational Safety and Health Administration (OSHA), might more appropriately perform the function. He said that he had since learned that RAC's prereview activity is unique; there is no OSHA mandate for such prior review. He felt the RAC's prereview process serves an important function. No other agency would perform this prereview should RAC extricate itself from the process.

He proposed, as an alternative proposal, that there be established a subcommittee of the RAC made up of some members of the RAC and some members of NIH staff with expertise in facilities and technologies, and that the subcommittee request representation from the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), the Center for Disease Control (CDC), and the Environmental Protection Agency (EPA). In this proposal, the subcommittee would review engineering and technology, and its review would be transmitted directly to the Director, NIH.

Dr. Goldstein seconded Dr. Krinsky's proposal. Dr. Gottesman did not accept the alternative proposal. Dr. Krinsky agreed to withdraw his motion with the understanding that it would be reconsidered later in the meeting.

Ms. King stated that Dr. Gottesman's proposal is an acceptable compromise, although she would prefer that the RAC withdraw from all review of industrial proposals. Dr. Mason noted that the RAC doesn't monitor even small-scale experiments. Dr. Gottesman said that the crux of the issue is whether evaluation of individual physical containment facilities by RAC is appropriate; she said it is not. Dr. Berns said that the RAC should consider only the biology of the systems. Dr. Goldstein supported Dr. Krinsky's proposal; he said that there is not enough information available on local IBCs.

Dr. Logan of OSHA felt RAC prereview of industrial applications serves an important function. He said that potential problems have been identified by RAC, and he hoped the RAC would consider Dr. Krinsky's proposal.

It was suggested that Dr. Gottesman's proposal could be divided and the last sentence of the motion voted on separately. Dr. Gottesman did not agree. Dr. Williams supported Dr. Gottesman's position saying he preferred to vote on the entire proposal. Ms. King agreed.

Mr. Thornton called the question on Dr. Gottesman's motion. The RAC accepted the language as published in the Federal Register (931/7) by a vote of twelve in favor, five opposed and one abstention. Dr. Goldstein requested that his vote of opposed be recorded. Dr. Ahmed also requested that his vote of opposed be recorded saying he is opposed to a voluntary compliance scheme.

VI. PROPOSED AMENDMENT OF SECTION IV-E-2

Ms. Cason introduced the proposal (tab 918, 931/11/A) by Dr. Irving Johnson of Eli Lilly and Company to amend Section IV-E-2 of the Guidelines.

Ms. Cason recounted the history of the proposal. She noted that several proposals to amend the Guidelines were submitted by Dr. Johnson for evaluation at the June 5-6, 1980 RAC meeting. Consideration of some of these proposals had been deferred. She said Dr. Johnson has resubmitted two of those deferred proposals for consideration at the September 6-7, 1980 meeting. One proposal would insert the following language after the first sentence of the second paragraph of IV-E-2:

"Appropriate representatives of industry shall also be chosen to provide expertise in fermentation technology, engineering, and other aspects of large-scale production."

Ms. Cason said that when this proposal was discussed at the June 1980 meeting, objections were raised to inclusion of the words "of industry." A motion recommending the following modified language was passed at the June 1980 meeting:

"Members should be chosen to provide expertise in fermentation technology, engineering and other aspects of large-scale production."

She said further discussion of the modified language had been deferred to the September 1980 meeting. Ms. Cason said the appointment of a member with fermentation technology expertise would afford RAC an additional dimension, and moved approval of the modified language.

Dr. Krinsky asked whether Ms. Cason's proposal might more appropriately be evaluated after his proposal to form a subcommittee has been discussed.

Dr. Gottesman replied that RAC has developed large-scale guidelines and would continue to review large-scale applications. Fermentation technology expertise would be desirable whether or not a subcommittee as proposed by Dr. Krinsky is established.

Dr. Johnson said he had inserted the words "representatives of industry" in his proposal as most expertise in this area is in industry or in academia consulting for industry. Dr. Campbell said he did not regard himself as a "representative" of academic biology but as an individual with certain expertise. He said he objected to the language of Dr. Johnson's proposal.

By a vote of thirteen in favor, two opposed and two abstentions the RAC recommended the language proposed by Ms. Cason, i.e.:

"Members should be chosen to provide expertise in fermentation technology engineering and other aspects of large-scale production."

VII. PROPOSED BIOSAFETY GUIDELINES FOR BIOMEDICAL LABORATORIES

Dr. John Richardson of CDC said the proposed guidelines (tab 915) are a more comprehensive listing of microorganisms than the 1974 CDC Classification of Etiologic Agents on the Basis of Hazard. He said the proposed biosafety guidelines designate four biosafety levels which correspond closely to the P-levels of the NIH Guidelines for Research Involving Recombinant DNA Molecules. The CDC guidelines propose three categories of laboratory activities (1) manipulation of small quantities or low concentrations of the agent, (2) manipulation of large quantities or high concentrations of the agent, and (3) manipulation of vertebrate animals infected with the agent. Ten thousand copies of the proposed biosafety guidelines will be distributed for comment.

Dr. Berns asked Dr. Richardson to comment on the status of the CDC guidelines. Dr. Richardson replied that the CDC guidelines are voluntary. He said that the Department of Health and Human Services (HHS) does not have the authority to impose such guidelines as on an intrastate basis.

VIII. PROPOSED PROCEDURES FOR REVIEW OF LARGE SCALE APPLICATIONS (Continued)

Dr. Krinsky returned to the concept which had been discussed previously (Section V) of a new RAC Subcommittee to deal with large-scale proposals. He would have the Subcommittee membership include RAC members as well as members from NIH and other agencies who have expertise in large-scale

fermentation technology. He suggested it be indicated that approval for facilities does not in any way suggest that there is an enforcement operation.

The question was posed whether the proposed subcommittee would review the physical containment aspects of individual large-scale applications after RAC has evaluated biological containment. Dr. Krinsky said it would; the RAC would review the biology of the systems, the subcommittee would subsequently review the physical containment, surveillance, monitoring, etc. It was suggested that a straw vote be taken on the concept. By a straw vote of eight in favor to three opposed, the RAC supported the concept, and it was agreed that more precise language would be developed for further consideration. (Discussion of this proposal continues in Section XVI).

IX. PROPOSED CHANGES IN REGISTRATION REQUIREMENTS

Dr. Maxine Singer introduced her proposal (tabs 917, 931/8, 934, 935, 938, 942-948, 952) to amend administrative requirements of the Guidelines. Dr. Singer said her proposal was intended to (1) eliminate the requirement for central registration of recombinant DNA projects at NIH, and (2) disengage the review of recombinant DNA proposals from the grant review process. She felt that safety is primarily maintained in the laboratory and reviewers close to the experimental locale render more meaningful review in terms of safety. She added that Genetic Manipulation Advisory Group (GMAG) in the United Kingdom has transferred the responsibility for categorization of most experiments to the local biosafety committees (tab 950).

Dr. Harris said that she believed that the NIH is approaching a point in experience and history where Dr. Singer's proposal would be reasonable. She noted that the issue revolves around RAC perception of and comfort with the sophistication and rigor with which IBCs pursue review. In light of the upcoming review of IBC performance she recommended delay until the IBC survey is completed.

Dr. Gottesman suggested that Dr. Singer's proposal could be divided into two parts; i.e., the elimination of registration with NIH, and the elimination of IBC prereview. Dr. Mason said he would feel comfortable eliminating NIH registration, but opposed allowing the investigator to bypass the IBC. Drs. Harris and Williams agreed with Dr. Mason.

Dr. Singer said that it is not the intent of her proposal to eliminate IBC review of registration documents. It would however allow the investigator to begin the experiment upon submission of the registration documents to the IBC, without waiting for IBC review. Dr. Goldstein expressed reservations; he noted that at the present time IBC effectiveness has not been fully evaluated. Dr. Fedoroff and Ms. King said they believed that IBCs are functioning well. Dr. Berns said he is aware of specific instances in which the investigator and the IBC disagreed on interpretation of the Guidelines. He opposed the elimination of IBC prereview.

Dr. Gottesman then moved the following three part proposal:

- (1) Eliminate the requirement for NIH review of IBC decisions on any experiments for which containment levels are specified in the Guidelines,
- (2) Defer consideration of eliminating prereview of experiments (by the IBC) until the frequency of principal investigator error in selecting the appropriate containment levels has been determined, and
- (3) IBCs keep records of recombinant DNA research done in the institution, including a record of the frequency of errors in classification of experiments by the principal investigator.

Ms. King seconded the motion.

Dr. Novick proposed that ORDA continue to receive, collect and evaluate MUAs during the interim period in which the IBC survey is being conducted. Dr. Gottesman did not accept this amendment to her proposal. Dr. Mason suggested that IBC function could be monitored without central registration.

Mr. Coley asked whether Dr. Singer's proposal might shut off lines of communication between local IBCs and ORDA. He noted some uncertainty at the IBC level in interpretation of the Guidelines. Dr. Singer replied that her proposal would not alter ORDA's advisory function to IBCs and principal investigators (PIs).

Dr. Campbell noted that the NIH Guidelines set minimal standards and that institutions, if they wish, may impose additional requirements beyond what the Guidelines require.

Dr. Fedoroff asked Dr. Gottesman why IBC review should be required, rather than letting the PI interpret the Guidelines. Dr. Gottesman replied that IBC prereview should continue for the following reasons: (1) IBC prereview would result in a more thorough review by individuals with varied perspectives; (2) The IBC has less of a conflict of interest in setting containment; (3) The IBC is more practiced in reading the Guidelines and evaluating proposals; and (4) RAC has some data suggesting that the IBCs function well, but no data on how correctly PIs evaluate containment levels.

The RAC then voted separately on the different parts of the motion.

The RAC voted fifteen in favor, three opposed, with no abstentions, to eliminate the requirement for NIH review of IBC decisions on any experiments for which containment levels are specified in the Guidelines. Dr. Goldstein wished to be recorded as voting against the proposal.

The RAC voted twelve in favor, five opposed, with one abstention, to defer consideration of eliminating pre-review of experiments by the IBCs until the frequency of principal investigator error in selecting the appropriate containment levels has been determined.

The RAC voted seventeen in favor, none opposed, with one abstention, that IBCs maintain records of recombinant DNA research done in their institution, including a record of the frequency of errors in classification of experiments by the principal investigator. Dr. Krinsky wished to be recorded as abstaining from the vote.

Dr. Singer pointed out that the language of Dr. Gottesman's proposal did not eliminate the requirement for registration with NIH. Dr. Gottesman moved a fourth provision, as follows:

"the IBCs no longer need register with NIH, recombinant DNA experiments for which containment levels are specified in the Guidelines"

Dr. Ahmed proposed to amend Dr. Gottesman's proposal so that NIH be required to collect, on a periodic basis, information from IBCs regarding all recombinant DNA research being conducted, and that this information be made available for public inspection. Dr. Gottesman did not accept Dr. Ahmed's amendment. Dr. Ahmed agreed to reoffer his amendment following a vote on Dr. Gottesman's motion. The RAC voted fifteen in favor, three opposed, with no abstentions that the IBC no longer need register with NIH, recombinant DNA experiments for which containment levels are specified in the Guidelines. Dr. Goldstein wished to be recorded as voting against the motion.

Dr. Ahmed then moved that there should be an annual summary report by the IBC to NIH on all recombinant DNA research at the institution. Dr. Novick did not consider it necessary to report exempt experiments. Dr. Ahmed wished to include all recombinant DNA experiments. The RAC voted against the motion by a vote of three in favor, thirteen opposed.

X. UPDATE OF NIH PROGRAM TO ASSESS THE RISKS OF RECOMBINANT DNA RESEARCH

Dr. Krause directed the committee to tab 933, the proposed first annual update of the NIH Program to Assess the Risks of Recombinant DNA Research. Dr. Krause reviewed the history of the program. The Secretary of Health, Education and Welfare (HEW) requested that the NIH prepare a risk assessment plan, that RAC review it, that it be published in the Federal Register for comment, made final, and that it be updated annually.

Dr. Krause said the Risk Assessment Program collects and analyzes data on potential hazards of recombinant DNA organisms. Dr. Krause reviewed progress on the issues developed at the Pasadena, California risk assessment meeting held in April 1980. He said a Request for Proposals (RFP), to determine if mice can mount an antibody response to insulin produced by E. coli host-vector systems, will be presented to the NIAID Advisory Council in the near future. In addition, a Request for Grant Applications (RFA) developed in conjunction with the National Institute of Arthritis, Metabolism and Digestive Diseases to investigate the absorption of peptide hormones by the intestine will soon be presented to the NIAID Advisory Council.

Dr. Krause reported that a contract has been awarded to the University of Minnesota to develop a comprehensive course on microbiological principles and techniques for work with potentially hazardous agents, including recombinant DNA organisms.

Dr. Krinsky asked if NIAID might prepare a review article on risk assessment on recombinant DNA. Dr. Krause said he would take this suggestion under

advisement. Dr. Nutter noted that the annual update synopsis information on the progress made during the year. Dr. Goldstein supported Dr. Krinsky's position saying that such a review would be valuable. Dr. Williams pointed out that the update contains a summary and that full reports had been published in the Recombinant DNA Technical Bulletin and in refereed journals. Dr. Wright requested that the update be footnoted and the sources cited. Dr. Krause invited individual comments from all RAC members during the 90 day public comment period.

XI. PROPOSED HV2 BACILLUS SUBTILIS HOST-VECTOR SYSTEMS

Dr. Campbell noted that the request (tab 931/4, 936) of Dr. William F. Burke, Jr., of Arizona State University, to certify Bacillus subtilis strain ASB298 as the host component of an HV2 host-vector system had been discussed at the June 1980 meeting. He said the RAC had requested additional data on DNA transfer by transformation from ASB298 to other Bacilli. Dr. Burke provided supplemental information demonstrating: (1) in soil, plasmid pBD64 does not transform competent B. subtilis under conditions where chromosomal DNA transforms 40% of competent recipient cells; (2) plasmid-bearing wild-type B. subtilis donates a barely detectible number of plasmids to competent recipient bacteria in the soil, whereas no transfer from ASB298 was detected; and (3) under optimal laboratory conditions, ASB298 donates a chromosomal marker at barely detectible levels.

Dr. Campbell questioned whether plasmid transformation frequency had been measured under optimum conditions, as the recipient bacteria did not contain homologous plasmids. Dr. Gottesman moved that ASB298 be certified as the

host component of an HV2 system on the basis of (1) the poor survivability of the strain; (2) its poor ability to donate DNA for transformation; (3) the high probability that plasmid vectors will transform very poorly.

The vector components would be the plasmid vectors already approved for HVL Bacillus subtilis systems. The motion was adopted by a vote of fourteen in favor, none opposed and two abstentions.

XII. PROPOSED REVISION OF SUBSECTIONS OF SECTION III-C-1-e

Dr. Berns presented the history of the proposal (tab 920, 931/6) to revise Section III-C-1-e-(1)-(b) of the Guidelines. A notice appeared in the Federal Register of January 31, 1980 concerning proposed revision of Section III-C-1-e, and its subsections. It was recommended that Sections III-C-1-e, III-C-1-e-(1), III-C-1-e-(1)-(a), and III-C-1-e-(1)-(b), of the Guidelines be changed and that a new Section III-C-1-e-(1)-(c) be added. Section III-C-1-e-(2) would remain unchanged. The RAC, at its March 6-7, 1980 meeting, recommended adoption of Sections III-C-1-e, III-C-1-e-(1), and III-C-1-e-(1)-(a) as published in the Federal Register of January 31, 1980 with certain modifications in Section III-C-1-e-(1)-(a).

The Director, NIH, accepted this recommendation and promulgated the following sections in the Federal Register of April 14, 1980:

"III-C-1-e. All Viral Vectors.

III-C-1-e-(1). Other experiments involving eukaryotic virus vectors can be done as follows:

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

At the March 1980 meeting, the RAC deferred consideration of Sections III-C-1-e-(1)-(b) and III-C-1-e-(1)-(c) pending accumulation of additional data. A working group met on May 13, 1980 in Miami Beach, Florida to discuss appropriate containment for experiments in which less than two-thirds of a eukaryotic viral genome is rescued with helper virus. The language developed by the working group appeared in the Federal Register of August 21, 1980:

"III-C-1-e-(1)-(b). Recombinants with less than two-thirds of the genome of any eukaryotic virus may be rescued with a helper virus using P2 containment if wild type strains of the virus are CDC Class 1 or 2 agents, or using P3 containment if wild type strains of the virus are CDC Class 3 agents (1)."

Dr. Berns moved acceptance of the language in the Federal Register.

Dr. Gottesman asked if the levels specified in the working group proposal were higher or lower than the case-by-case assignments which have been made to date under the current Section III-C-1-e-(1)-(b). Dr. Barban replied

that in the use of SV40 in some rescue experiments, containment is currently P3, and would, if this proposal were adopted, be P2.

Dr. Novick asked Dr. Berns to review the issues. Dr. Berns said the major consideration is whether splicing of various viral genomes might produce a pathogen more dangerous than the parent viruses themselves. The working group consensus was that no indication suggested this possibility.

Dr. Berns said viruses are the product of millions of years of evolution, and are selected for optimal function.

By a vote of ten in favor, five opposed and one abstention, the RAC recommended the revision of Section III-C-1-e-(1)-(b) of the Guidelines as published in the Federal Register on August 21, 1980.

XIII. REQUEST TO INCLUDE VIBRIO CHOLERAE IN APPENDIX A

Dr. Gottesman presented the request (tab 909, 931/12) of Dr. John A. Mekalanos of Harvard Medical School to add Vibrio cholera to sublist A, Appendix A of the Guidelines. She said Dr. Mekalanos has presented data showing evidence of R factor transfer. Dr. Gottesman said that recombinant DNA experiments between organisms within each sublist of Appendix A are exempt from the Guidelines under Section I-E-4. Section I-E-4 exempts "certain specified recombinant DNA molecules that consist entirely of DNA segments from different species that exchange DNA by known physiological processes..."

Dr. Gottesman said a discussion has continued concerning the criteria required to qualify organisms for inclusion in Appendix A. She said the issue revolved on whether R factor transfer was sufficient or whether

evidence of chromosomal exchange should be required. Committee members have previously argued that where R factor exchange occurs, chromosomal exchange, if looked for assiduously, probably would be found. She said she has differed with the committee on this interpretation, and that her inclination would be to require evidence of chromosomal transfer.

Dr. Novick expressed some concern over the pathogenic nature of Vibrio cholera but qualified his statement with the following points: (1) a virulent E. coli producing cholera toxin probably would not be worse than a virulent E. coli producing E. coli endotoxin; and (2) cholera toxin is processed in V. cholera; E. coli may not be able to produce an active toxin. He suggested that certain experiments might be permitted under P1 + EK1 containment conditions, but that V. cholera should not be added to Sublist A of Appendix A. Dr. Mason concurred.

Dr. Campbell said he accepted R-factor exchange as evidence that chromosomal exchange is occurring and moved approval of Dr. Mekalanos' request. He said that the toxin question is covered by prohibition I-D-2.

Dr. Mason questioned whether RAC could vote on this issue in the absence of a definition of a "potent" toxin. Dr. Novick moved that Vibrio cholera be added to Sublist A, Appendix A, but that deliberate cloning of toxin genes be excluded. Dr. Campbell accepted the amendment. The vote was five in favor, four opposed and five abstentions.

Mr. Thornton suggested that the issue be reconsidered as the sentiment of the committee was clearly divided. By a vote of eleven in favor, one

opposed, the RAC agreed to reconsider the previous vote. Dr. Mason then moved to defer action on the proposal until additional information is available on the experiments being proposed. By a vote of thirteen in favor, one opposed, the RAC deferred action on Dr. Mekalanos' proposal.

XIV. PROPOSED AMENDMENT OF APPENDIX E OF THE GUIDELINES

Dr. Campbell said that Dr. Fritz Reusser of The Upjohn Company requested (tab 916, 931/9) that two entries under Appendix E be amended to permit specified experiments be performed with additional Streptomyces species. Dr. Campbell suggested that each of the proposals be considered separately. The first proposal is as follows:

"Bacillus subtilis strains that do not carry an asporogenic mutation can be used as hosts specifically for the cloning of DNA derived from E. coli K-12 and Streptomyces coelicolor, S. aureofaciens, S. rimosus, S. griseus, S. cyaneus, and S. venezuelae using NIH-approved Staphylococcus aureus plasmids as vectors under P2 conditions."

Dr. Campbell, recommended approval of the proposal. By a vote of fourteen in favor, none opposed and three abstentions, the RAC adopted this proposal.

Dr. Reusser's second proposal is as follows:

"Streptomyces coelicolor, S. aureofaciens, S. rimosus, S. griseus, S. cyaneus and S. venezuelae can be used as hosts for the cloning of DNA derived from B. subtilis, E. coli K-12, or from S. aureus

vectors that have been approved for use in B. subtilis, under P2 conditions, using as vectors any plasmids indigenous to these Streptomyces species or able to replicate in these hosts by natural biological mechanisms."

Dr. Novick proposed that there should be a restriction limiting the type of plasmid vector allowed to be used. He proposed to amend the language to require use of "nonconjugative" plasmid vectors. Dr. Campbell accepted the amendment.

By a vote of fifteen in favor, none opposed and two abstentions the RAC recommended the following language:

"Streptomyces coelicolor, S. aureofaciens, S. rimosus, S. griseus, S. cyaneus, and S. venezuelae can be used as hosts for the cloning of DNA derived from B. subtilis, E. coli K-12 or from S. aureus vectors that have been approved for use in B. subtilis, under P2 conditions, using as vectors any nonconjugative plasmids indigenous to these Streptomyces species or able to replicate in these hosts by natural biological mechanisms."

Dr. Novick asked if this modified language might restrict researchers already working under Appendix E. Dr. Taylor of Smith Kline and French Company replied that several investigators are developing conjugative plasmid vectors under this section of Appendix E. Dr. Novick suggested that more concrete language on this issue might be considered at the next meeting.

(Executive Secretary's note: The Director, NIH, in his decision deleted the requirement for use of "nonconjugative plasmids." The reasons for this decision are presented in the Federal Register of November 21, 1980).

XV. REQUEST FOR EXEMPTION OF STREPTOCOCCUS SANGUIS AND S. PNEUMONIAE UNDER SECTION I-E-4

Dr. Gottesman presented the proposal (tab 919, 927, 931/10) of Dr. Walter R. Guild of Duke University. Dr. Guild proposed that Streptococcus sanguis and Streptococcus pneumoniae be added to Appendix A of the Guidelines. Dr. Gottesman said the evidence for natural exchange of genetic material between the two organisms in both directions is good. She moved that these organisms be added to Appendix A as a new sublist.

By a vote of sixteen in favor, none opposed and one abstention, the committee adopted the proposal.

XVI. PROPOSED PROCEDURES FOR REVIEW OF LARGE-SCALE APPLICATIONS (Continued)

Mr. Thornton reminded the committee that it had earlier (Section V) adopted language defining the RAC's role in the review of large-scale proposals and that Dr. Krinsky (Section VIII) had proposed a new RAC subcommittee be involved in the review.

Dr. Krinsky moved the following language:

"An industrial review subcommittee of the RAC shall be established with the responsibility for advising the Director on procedures

and facilities design pertaining to applications for large-scale operations.

"After the full RAC has reviewed the biological containment requirements for a large-scale proposal, the subcommittee shall examine the applicant's plans for large-scale operations and issue recommendations to the Director on plant design, health surveillance, and environmental monitoring. The Director shall advise firms of recommended design parameters and operational procedures. The determination shall not be construed as NIH certification of industrial operations.

"The subcommittee shall invite participation from NIH's biosafety staff, OSHA, NIOSH, CDC, Food and Drug Administration (FDA), EPA and the U. S. Department of Agriculture (USDA)."

Dr. Talbot pointed out that; (1) ad hoc "working groups" on specific issues can be established by the RAC Chairman; "subcommittees" can be established only by modification of the Committee charter, which requires approval of the Secretary of Health and Human Services.

Dr. Fedoroff expressed concern about the delays if first the full RAC, and then subsequently a subcommittee, were to be involved in the review process. Dr. Goldstein favored Dr. Krinsky's proposal as it would allow NIOSH, OSHA, etc. to participate more intimately in the decision making process.

Dr. Gottesman said that she was opposed to continuation of review of equipment design in individual applications by either the full RAC or a subcommittee.

Dr. McGarrity suggested that the American Society for Microbiology (ASM), might develop specifications for large-scale fermentors and auxiliary equipment to minimize personnel exposure and biohazards as has been done with safety specifications of laminar flow biological safety cabinets.

Dr. Johnson of Eli Lilly said that Dr. Krinsky's proposal contradicted the proposal passed by the RAC earlier (Section V). He expressed a belief that industrial large-scale growth of microorganisms affords higher levels of containment than procedures in university laboratories. Dr. Simon of Genex Corporation suggested that Dr. Krinsky substitute the word "institutions" for the word "firms" in his proposal. Dr. Krinsky agreed.

Dr. Mason suggested that the proposed subcommittee would have to advise the full RAC on each recommendation; if the subcommittee is empowered with final authority without reporting to the full RAC, he would not consider it to be a subcommittee of the RAC. A procedure involving a report to the full RAC would entail considerable delay. He said the RAC should either (1) accept responsibility for full RAC review of physical facilities or (2) delegate that authority to the IBC as voted by the RAC yesterday, the option he preferred.

Dr. Logan of OSHA opined that prereview of physical facilities serves an important function. He said the legal counsel of the Department of Labor (DOL) believes that OSHA does not have the authority to conduct such prereview. He further stated that the Federal Interagency Advisory

Committee on Recombinant DNA has no mandate to conduct this type of prereview. He said that if the RAC does not accept Dr. Krinsky's proposal, large-scale prereview of physical facilities will not occur. Dr. Berns asked if representatives of the various federal agencies would be able to legally vote in the proposed subcommittee. Dr. Logan said the legal counsel of the Department of Labor would have to determine the propriety of OSHA participation. Dr. Gottesman reminded the committee that under the proposal previously voted, the RAC will continue to review biological aspects of applications. Dr. Ahmed said that while he personally did not wish to participate in the review of confidential material, he thought the prereview system was valuable. He supported Dr. Krinsky's proposal.

Dr. McGarrity asked how other federal agencies view recombinant DNA experiments and products. Dr. Miller of FDA said it is likely there will be some linkage between the FDA product approval process and compliance with other federal guidelines, including the NIH Guidelines for Research Involving Recombinant DNA Molecules. Dr. Logan said that NIOSH and OSHA were working closely to develop a plan for possible regulation, or at least procedures to protect safety and health.

Dr. Campbell said that the RAC has certain responsibilities. One such responsibility is to set and to revise standards, e.g., what constitutes Pl-LS. A second responsibility is to monitor the functioning of the system. He said he would support Dr. Krinsky's proposal if the subcommittee was constituted to gather information and to advise RAC on large-scale technology, but not to perform review of individual projects.

Dr. Gottesman moved that the motion be amended to read as follows:

"An industrial review subcommittee of the RAC shall be established with the responsibility for advising the full RAC on procedures and facilities design pertaining to applications for large-scale operations. The subcommittee shall invite participation from NIH's biosafety staff plus OSHA, NIOSH, CDC, EPA, and USDA."

The subcommittee would not review individual proposals, but would review standards. Dr. Berns suggested that Dr. Gottesman's proposed language be amended to change the name of the subcommittee to the "Large-Scale Review Subcommittee." Dr. Gottesman accepted this amendment. Mr. Thornton asked Dr. Krinsky if he would accept Dr. Gottesman's amended language as an amendment to his original motion. Dr. Krinsky declined. Instead, Dr. Krinsky moved to amend Dr. Gottesman's amendment to read as follows:

"A large-scale review subcommittee of the RAC shall be established with the responsibility for advising the entire RAC on large-scale standards and the Director of NIH on procedures and facilities design for large-scale operations.

"After the full RAC has reviewed the biological containment requirements for a large-scale proposal, the subcommittee shall examine the applicant's plans for large-scale operations and issue recommendations to the Director on plant design, health surveillance, and environmental monitoring. The Director shall advise institutions of recommended

design parameters and operational procedures. The determination shall not be construed as NIH certification of industrial operations.

"The subcommittee shall invite participation from NIH's Biosafety Division, OSHA, NIOSH, CDC, FDA, EPA and USDA."

Dr. Krinsky said that it is the intent of his motion that the subcommittee will deal with prereview of individual applications. Dr. Federoff said that Dr. Krinsky's proposed language would introduce delays in the procedure.

Mr. Thornton called the question on Dr. Krinsky's proposed amended language. By a vote of three in favor, fifteen opposed, the RAC opposed Dr. Krinsky's proposed amended language.

Mr. Thornton then returned to Dr. Gottesman's proposed amended language. It was suggested that the words "...pertaining to large-scale operations" be substituted for the words "...pertaining to applications for large-scale operations" in the first paragraph of the motion. Dr. Gottesman agreed. It was reiterated that the subcommittee would not perform prereview of individual applications.

Mr. Thornton then called the vote on Dr. Gottesman's amendment to Dr. Krinsky's original motion. By a vote of thirteen in favor, four opposed and one abstention, the RAC agreed to the amendment.

Dr. Campbell offered an amendment to add the words "and on the performance of local IBCs in reviewing physical containment facilities." The amended motion would read as follows:

"A large-scale review subcommittee of the RAC shall be established with responsibility for advising the RAC on procedures and facilities design pertaining to large-scale operations, and on the performance of local IBCs in reviewing physical containment facilities. The subcommittee shall invite participation from NIH's biosafety staff plus OSHA, NIOSH, CDC, FDA, EPA and USDA."

Dr. Campbell explained that this provision would permit a review of how well IBCs are performing this function. Dr. Gottesman noted NIAID is planning to evaluate IBC function. She questioned whether a special effort was required in large-scale applications. Dr. Campbell said that the proposed subcommittee would have the expertise to evaluate this aspect of IBC function. By a vote of thirteen in favor, three opposed and two abstentions the RAC accepted the Campbell amendment.

The RAC then voted fifteen in favor, two opposed and two abstentions to adopt the following amended proposal:

"A large-scale review subcommittee of the RAC shall be established with responsibility for advising the RAC on procedures and facilities design pertaining to large-scale operations, and on the performance of local IBCs in reviewing physical containment facilities. The subcommittee shall invite participation from NIH's biosafety staff plus OSHA, NIOSH, CDC, FDA, EPA and USDA."

XVII. PROPOSED CONTAINMENT FOR CLONING AMONG MEMBERS OF THE ACTINOMYCETES GROUP

Dr. Brill introduced the request (tab 925, 926, 931/14) of Dr. Dean Taylor of the Smith, Kline and French Laboratories. Dr. Taylor proposed that the third entry in Appendix E of the Guidelines be modified to read:

"P2 physical containment shall be used for DNA recombinants produced between members of the Actinomycetes group except for those species which are known to be pathogenic for man, animals or plants."

This proposal was made previously by the RAC Working Group on Prokaryotic Host-Vectors Other Than E. coli and appeared in the Federal Register, April 13, 1979, 44 (73): 22316. The RAC considered the proposal at its May 21-23, 1979 meeting and recommended to restrict this so that it did not include the entire Actinomycetes group but rather only the genera Streptomyces and Micromonospora. The Director, NIH, accepted this recommendation and the action was published in the Federal Register, July 20, 1979, 44 (141): 42916, and appears as the third entry in Appendix E of the Guidelines.

Dr. Brill noted that currently the Guidelines permit P2 containment to be used for DNA recombinants produced between Streptomyces and Micromonospora. Experiments using other genera of the Actinomycetes may be performed under P3 containment. He said there are few pathogenic organisms in the Actinomycetes genera and most of those organisms are pathogenic only in compromised hosts. He moved approval of the proposal. Dr. Scandalios concurred.

Dr. Taylor said pathogenic Actinomycetes are marginal pathogens; the hosts are generally compromised.

Mr. Thornton introduced Dr. Vee J. Gill of the Department of Clinical Pathology, NIH. Dr. Gill said that many genera of the Actinomycetes are not pathogenic for man, animals and plants.

Drs. Gill and Taylor said that experiments to demonstrate exchange among Actinomycetes have not been performed to any great extent. Dr. Novick said that among the Streptomycetes, genetic exchange, if sought, is usually found.

Dr. Krinsky said that three categories of organisms can be considered: (1) those organisms known to be pathogens, (2) those organisms known not to be pathogens, and (3) those for which insufficient data exists to determine whether they are pathogens or nonpathogens. He suggested that the language of the proposal should be restricted to permit P2 containment only for known nonpathogens. Dr. Gill said it would be difficult to establish a list of nonpathogens; certain organisms might or might not be included on the list depending on the definition of pathogenicity. She said two Streptomycyces species, currently included in Appendix E, have been reported to cause infections.

Dr. Krinsky proposed that the motion be amended to read as follows:

"P2 physical containment shall be used for DNA recombinants produced between members of the Actinomycetes group which are known not to be pathogenic to man, animals or plants."

Dr. Brill said he would not accept the amendment. He said hundreds of thousands of Actinomycetes soil isolates had been screened in attempts to isolate antibiotic producers without any known disease having been caused in laboratory workers; past history says that they are safe. Dr. Berns asked why P2 containment was being proposed. Dr. Taylor said Actinomycetes are generally manipulated under P2 conditions; the organisms grow slowly and P2 containment is used to prevent contamination.

Mr. Thornton called the question on the amended language proposed by Dr. Krinsky. By a vote of three in favor, eleven opposed, and three abstentions, the RAC turned down the proposed amendment.

Mr. Thornton then called the vote on the language appearing in the Federal Register. By a vote of sixteen in favor, one opposed and one abstention the RAC adopted the language published in the Federal Register, as follows:

"P2 physical containment shall be used for DNA recombinants produced between members of the Actinomycetes group except for those species which are known to be pathogenic for man, animals or plants."

XVIII. PROTOCOL REQUIRING ASSIGNMENT OF CONTAINMENT LEVELS

Dr. Brill introduced a request (tab 941) from Dr. Dean Taylor of Smith Kline and French Laboratories. Dr. Taylor proposed to transform protoplasts of Streptosporangium with a plasmid vector constructed to contain (1) the E. coli plasmid pBR322, (2) a Streptosporangium plasmid, pS_GB-1, (3) an antibiotic resistance determinant from Streptomyces species or HVI approved Bacillus subtilis cloning vectors, and (4) flanking sequences from the Streptomyces plasmid vector from which the determinant is isolated. A letter from the CDC stating that the species may reasonably be treated as a Class 1 agent had been appended to Dr. Taylor's request.

Dr. Brill moved approval at P2 physical containment. Dr. Scandalios seconded the motion. By a vote of seventeen in favor, none opposed, and one abstention the RAC adopted the proposal.

XIX. PROPOSED AMENDMENT OF SECTION IV-E-2

Mr. Thornton then called the attention of the RAC to part two of a proposal (tab 918, 931/11/B) from Dr. Irving Johnson of Eli Lilly and Company to add a new Section IV-E-2-b to the Guidelines as follows:

"A permanent subcommittee of the RAC shall be responsible for advising the Director, NIH, on the actions, listed in Section IV-E-1-b-(3)-(d) pertaining to large-scale applications. Submissions that are in compliance with the Guidelines may be recommended by the subcommittee to the Director of NIH for approval. The subcommittee shall also be authorized to consider preliminary plans for large-scale operations

and to recommend approval contingent upon completion of the large-scale facility according to those plans. The subcommittee will be responsible for expeditiously processing applications."

Ms. Cason noted that earlier in the meeting (Section XVI) the RAC had voted to establish a large-scale review subcommittee. She moved to table discussion of this proposal. By a vote of fourteen in favor, three opposed, the RAC agreed to table further discussion of the proposal.

XX. MINOR MODIFICATIONS OF LARGE-SCALE PROTOCOLS

Dr. Gottesman said that at the last meeting the Working Group on Large-Scale Procedures had presented a proposal for dealing with minor modifications of previously approved large-scale protocols. She said objections to aspects of the proposal had been raised, and the RAC had voted to defer further discussion until this meeting. She felt any proposal should address the following issues:

- (1) What type of expedited procedure should be developed to deal with minor modifications of previously approved large-scale protocols and
- (2) What criteria should be applied to determine if a modification is indeed minor.

She said she had not composed specific language to present to the RAC but wished to express her general thoughts, and hoped to obtain a sense of the committee. She suggested that a formal subcommittee, or a working group, or several reviewers selected by ORDA, could evaluate the applications to

determine whether they involve minor modifications of an already approved proposal. If so, the package could be sent to the Director, NIH for approval without review by the full RAC. She said the individuals responsible for the review would have two responsibilities:

- (1) To determine if the modification is indeed a minor modification. If one reviewer does not agree that the modification is minor, the proposal would be evaluated by the full RAC;
- (2) If the reviewers unanimously agree the modification is minor, the review group would determine whether the modification significantly affects any containment aspect of the parent proposal. She said the RAC might construct some guidelines in this area, e.g., the general acceptability of deletions, single base changes, additions of short segments that do not lead to production of new products, change to an equivalent vector, etc.

Dr. Gottesman said that while it would be extremely difficult in advance to imagine every possible change and its consequence, it will, in most cases, be obvious to the reviewers when a specific proposed modification is minor. She felt several RAC members involved in evaluating the original parent proposal should be involved in review of any proposed minor modifications. After discussion of various aspects of the proposal, Dr. Gottesman agreed to formulate a specific proposal for consideration at the January 1981 meeting.

XXI. REQUEST FOR CERTIFICATION OF HVI BACILLUS SUBTILIS HOST-VECTOR SYSTEM

Dr. Brill introduced a request (tab 921, 931/5) of Dr. David B. Wilson of Cornell University. He said Dr. Wilson requests HVI certification of a host-vector system based on certified host-components of HVI Bacillus subtilis host-vector systems and a plasmid, pAB124, isolated from Bacillus stearothermophilus. Dr. Brill said Bacillus stearothermophilus is not a pathogen. He recommended that the plasmid be approved for use with certified HVI Bacillus subtilis hosts.

By a vote of eighteen in favor, none opposed, the RAC recommended that plasmid pAB124, isolated from Bacillus stearothermophilus, be certified for use with HVI certified Bacillus subtilis hosts, as an HVI host-vector system.

XXII. PROTOCOLS REQUIRING ASSIGNMENT OF CONTAINMENT LEVELS

A. Requests for permission to transform Chlamydomonas reinhardi with E. coli/S. cerevisiae plasmids

Dr. Brill introduced the requests (910, 911, 931/1) of Dr. John Carbon of the University of California, Santa Barbara, and Dr. Stephen Howell, University of California, San Diego. He said these investigators request permission to use the unicellular flagellate Chlamydomonas reinhardi, under P2 physical containment, to clone defined DNA segments derived from E. coli and S. cerevisiae using E. coli/S. cerevisiae hybrid vectors.

Dr. Brill said Chlamydomonas reinhardi is the most studied green alga, and has not been demonstrated to be a pathogen or to produce toxins.

He moved approval of the proposal. Dr. Scandalios concurred and added that the organism does not freely exchange DNA with other species.

By a vote of sixteen in favor, none opposed and one abstention, the RAC adopted the motion to approve the requests.

B. Request for Permission to Transform *Candida albicans* with *E. coli*/
S. cerevisiae Hybrid Plasmids

Dr. Maas introduced the requests (tab 912, 913, 928, 931/2) of Dr. P. T. Magee of Michigan State University and Dr. W. LaJean Chaffin of Texas Tech University. The investigators had requested consideration of the appropriate containment level for the return of *Candida albicans* DNA to the host of origin. The *Candida albicans* DNA will be cloned in an Ekl *E. coli* K-12 or in a laboratory strain *S. cerevisiae* employing a hybrid *E. coli*/*S. cerevisiae* plasmid vector, or the *S. cerevisiae* 2 micron plasmid.

Dr. Maas said *Candida albicans* is an opportunistic pathogen and is classified in the proposed revised CDC Biosafety Guidelines as a Class 2 etiological agent. He said the investigators hope to analyze the genetics of the organism using recombinant DNA techniques. Ultimately they hope to elucidate the basis of *C. albicans* pathogenicity.

Dr. Pinon suggested that P2 containment is adequate. He said *Candida* does not produce toxins; in addition it is non-invasive. *Candida albicans* inhabits mucosal membranes, and is considered a normal component

of the microflora. Anywhere from 25 to 100% of the population, carry Candida.

Dr. Novick pointed out that Candida can cause disease in individuals receiving broad spectrum antibiotics. Dr. Gottesman said this is essentially a return to host of origin experiment, and felt the relevant question is whether the S. cerevisiae DNA introduced into Candida might contribute to Candida pathogenicity.

Dr. Pinon moved that the experiments proposed by Drs. Magee and Chaffin be permitted at the P2 level of containment. By a vote of fourteen in favor, one opposed, and three abstentions the RAC approved the motion.

XXIII. INSTITUTIONAL BIOSAFETY COMMITTEE (IBC) SURVEY (Continued)

Dr. Novick requested an opportunity briefly to address the RAC concerning the proposed NIAID evaluation of IBC functions which had been discussed earlier in the meeting (Section IV). He said he would like the RAC to go on record as requesting that the RFP being developed include the following:

- (1) An evaluation of MUAs or registration documents submitted to IBCs for compliance with the Guidelines, and
- (2) An inquiry of how often physical facilities are inspected by IBCs, and the results of the inspections.

Dr. Goldstein supported Dr. Novick's proposal; he said Dr. Dutton showed the performance of individual IBCs is highly variable. Dr. Gottesman objected to an evaluation of every registration document; she and Dr. Berns

thought a sampling procedure might be more appropriate. Dr. Krinsky said that practices for social science research usually involved random sampling. He favored telling the contractor what was to be evaluated, and leaving it to the contractor to use the state of the art of evaluation research to accomplish the task.

It was agreed that Dr. Nutter will be asked to discuss the draft RFP with the RAC at its January 1981 meeting, prior to the RFP being issued.

XXIV. DISCUSSION OF INCIDENT AT UNIVERSITY OF CALIFORNIA, SAN DIEGO

Dr. Goldstein wished to discuss the recent events at the University of California, San Diego (UCSD) concerning an apparent infraction of the NIH Guidelines. He said he was disturbed that the first report of the problem came up in January and the IBC did not consider the issue until July. Dr. Talbot recounted the history of the incident as detailed in tab 929. He said in January 1980, several graduate students informed Dr. Ian Kennedy at the University of California, San Diego, of their suspicions that the Guidelines were being violated. Only in May did the students speak of this to the biology department chairman. The department chairman obtained a sample of the virus. The sample was sent to the California State Department of Health Services for testing. On July 22, 1980, the results were reported to UCSD; the vial contained Semliki Forest Virus rather than Sindbis Virus. The IBC met on July 30, 1980 and immediately prohibited Dr. Kennedy from continuing recombinant DNA work. Dr. Talbot said that as detailed in tab 929, an NIH committee would meet on October 8, 1980 to review the incident and recommend what response NIH should take.

Dr. Talbot said that copies of the final recommendations of that committee will be sent to the RAC.

Dr. Krinsky asked why the apparent Guideline violation had occurred.

Dr. Talbot replied that the UCSD IBC report (tab 929) gives their conclusions, and that a reply to this report from Dr. Kennedy had just been received. Dr. Pinon added that Dr. Kennedy had recently resigned from UCSD and that a UCSD departmental committee had also submitted a report to the UCSD Chancellor.

Dr. Krinsky asked about the role of the RAC in dealing with instances of non-compliance with the Guidelines. Dr. Talbot replied that dealing with an individual case is a responsibility of NIH and not the RAC. If from the specific case there arise generic issues suggesting a revision of the Guidelines, the consideration of such revisions would be a RAC function.

XXV. PROTOCOLS REQUIRING ASSIGNMENT OF CONTAINMENT LEVELS

A. Proposal to Introduce Genes Cloned in E. coli K-12 into Arabidopsis Plants through the Use of Agrobacterium tumefaciens Carrying an E. coli/Ti Hybrid Plasmid Vector.

Dr. Brill introduced a proposal (tab 914, 931/3) from Dr. Donald J. Merlo of the University of Missouri-Columbia. Dr. Merlo, employing the following protocol, requested permission to introduce E. coli and Arabidopsis genes into Arabidopsis thaliana:

- (1) A hybrid plasmid vector, constructed from the E. coli plasmid pBR325 and the origin of replication and transfer genes of

Agrobacterium tumefaciens plasmid Ti, will be cloned into E. coli K-12.

- (2) Arabidopsis DNA will be introduced into the E. coli/Ti hybrid plasmid and cloned in E. coli K-12.
- (3) The thiamine gene of E. coli K-12 will be introduced into the E. coli/Ti vector carrying Arabidopsis DNA, and cloned in E. coli K-12.
- (4) The hybrid plasmid into which Arabidopsis DNA and the thiamine gene have been ligated will be transformed into Agrobacterium tumefaciens.
- (5) Agrobacterium tumefaciens will be used to introduce the E. coli/Ti plasmid vector carrying the E. coli thiamine gene and Arabidopsis DNA into Arabidopsis plants.

Steps (1) (2) and (3) are covered by Section III-O of the Guidelines and may be performed under P1 containment. Steps (4) and (5) are covered under entry four of Appendix E and may be conducted under P3 containment. Dr. Merlo requested permission to perform steps (4) and (5) at P1 or P2 containment.

Dr. Brill noted that Arabidopsis plants are easily contained. He said Agrobacterium tumefaciens is not a serious plant pathogen, as it only invades injured tissues. He moved that the investigator be permitted to perform steps (4) and (5) under P1 containment conditions.

Dr. Scandalios concurred.

Dr. Goldstein moved to amend Dr. Brill's motion to require P2 physical containment for steps (4) and (5). Dr. Brill did not accept the amendment. By a vote of four in favor, nine opposed, and three abstentions, the amendment was not accepted by RAC.

Mr. Thornton then called the vote on Dr. Brill's motion. By a vote of twelve in favor, two opposed and three abstentions, the committee accepted the motion to set containment at P1 for steps (4) and (5) of the proposed protocol.

B. Request for Consideration of Appropriate Containment for Experiments Involving *Zymomonas mobilis*

Dr. Maas introduced the request (tab 922, 931/13) from Drs. B. S. Montencourt and D. E. Eveleigh of Rutgers University to introduce into *Zymomonas mobilis*, DNA from non-pathogenic *Pseudomonas* strains that had been cloned in *E. coli* K-12.

Dr. Maas said that *Zymomonas mobilis* is a nonpathogenic anerobic soil bacterium which exchanges genes with *Pseudomonas aeruginosa* and *E. coli*.

Dr. Barban added that *Zymomonas mobilis* is frequently found in fermenting plant juices, principally in tropical climates.

Dr. Maas moved approval of the request under P2 conditions. By a vote of seventeen in favor, none opposed, the RAC adopted the motion.

C. Request to Clone Schizosaccharomyces pombe DNA in Schizosaccharomyces pombe

Dr. Brill introduced the request (tab 930, 931/15) of Dr. Benjamin Hall of the University of Washington to clone Schizosaccharomyces pombe DNA in Schizosaccharomyces pombe using approved HV1 Saccharomyces cerevisiae/E. coli hybrid plasmids as vectors. Dr. Hall requested P1 as the appropriate level of physical containment. He pointed out that Schizosaccharomyces pombe has been the subject of intense genetic studies in the laboratory and traditionally has been used to ferment beverages for human consumption.

Dr. Brill moved to approve the request under P1 conditions. Dr. Pinon concurred. By a vote of seventeen in favor, none opposed, the RAC accepted the motion.

D. Request for Permission to Clone the Tox A Gene of Staphylococcus aureus

Dr. Maas introduced the request (tab 940) of Drs. A. G. Barbour and L. W. Mayer of the National Institutes of Health to clone the pyrogenic exotoxin type A (Tox A) gene of Staphylococcus aureus. The issue is whether this is a prohibited experiment under the Guidelines.

Dr. Maas said Tox A produces fever, enhances susceptibility to E. coli endotoxin, stimulates immune system T cells, and enhances acquired skin reactivity to other antigens. He said Tox A is less potent than botulinum or tetanus toxin. He said Drs. Barbour and Mayer originally requested permission to clone the gene in an HV2 Bacillus subtilis host-vector

system, but when informed that no HV2 B. subtilis system had been certified to date, requested permission to clone the Tox A gene in an EK2 system. Dr. Maas noted that certification of an HV2 Bacillus subtilis had been recommended by the RAC at this meeting. He preferred that the B. subtilis host-vector system be used for cloning, as Tox A activates the E. coli endotoxin. He suggested that containment conditions specified for cloning toxin genes should be based on the pharmacological effect of the toxin. He urged caution in concluding that cloning a toxin gene from a mildly pathogenic organism in a non-pathogenic host-vector system will present no difficulties. He said toxin expression and potency depend on many variables. He said, however, that he did not consider Tox A to be a potent toxin.

Dr. Berns said pyrogenic Staphylococcus aureus is a potent pathogen. Dr. Nightingale concurred.

Dr. Gottesman said the issue is whether Tox A is a potent toxin; if it is not, P1 + EK1 containment is indicated by the Guidelines for cloning in E. coli K-12. Dr. Novick said he was concerned that toxins which are not "potent" may be cloned at P1 + EK1 containment.

Dr. Gottesman moved that, as the RAC is currently in the process of reassessing the cloning of toxins under the Guidelines, the proposed experiments be approved in E. coli K-12 systems under P3 + EK2 conditions, or at P3 + HV2 with a Bacillus subtilis system. By a vote of seventeen in favor, none opposed, the RAC adopted Dr. Gottesman's motion. (Executive

Secretary's Note: The Director, NIH, in his decision limited cloning of the Tox A gene to HV2 Bacillus subtilis host-vector systems under P3 containment for the present time.)

E. Request for Permission to Construct an E. coli/H. Influenzae Hybrid Plasmid for Use in H. Influenzae

Dr. Gottesman introduced the proposal (tab 959) from Dr. Hamilton Smith of the Johns Hopkins University. Dr. Smith wishes to insert an E. coli gene coding for tetracycline resistance (Tn10) into the Haemophilus influenzae plasmid pRSF0885. The plasmid construct would be used in Haemophilus influenza strain Rd to clone Haemophilus genes.

Dr. Campbell moved to approve the experiments under P1 conditions. By a vote of twelve in favor, none opposed and seven abstentions, the RAC adopted the motion.

XXVI. FUTURE MEETING DATES

Dr. Gartland called the committee's attention to tab 951 which lists future meeting dates. He said the meeting which had been planned for December 1981 had been rescheduled to January 1982.

XXVII. CLOSED SESSION

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

XXVIII. ADJOURNMENT

The meeting adjourned at approximately 4:40 p.m., Friday, September 26, 1980.

Respectively submitted,

Elizabeth A. Milewski, Ph.D.
Rapporteur

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