NATIONAL CANCER ADVISORY BOARD

convened on February 3-4, 1998, at the:
National Institutes of Health
Natcher Building, Room E1 and E2
Bethesda, Maryland 20892

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The National Cancer Advisory Board (NCAB) convened for its 105th regular meeting at 9:00 a.m., February 3, 1998, in the Natcher Building, Room E1 and E2, National Institutes of Health.

NCAB MEMBERS

Dr. J. Michael Bishop (Chairperson)
Dr. Richard J. Boxer (absent)
Mrs. Zora K. Brown
Dr. Pelayo Correa
Dr. Robert W. Day
Dr. Kay Dickersin
Mrs. Barbara P. Gimbel (absent)
Dr. Alfred L. Goldson
Dr. Frederick P. Li
Dr. Sandra Millon-Underwood
Dr. Ivor Royston
Dr. Philip S. Schein
Dr. Phillip A. Sharp
Dr. Ellen V. Sigal

Ms. Ellen L. Stovall
Dr. Vainutis K. Vaitkevicius
Dr. Charles B. Wilson

President's Cancer Panel

Dr. Harold P. Freeman (Chairperson)
Dr. Paul Calabresi
Ms. Frances Visco (absent)

Alternate *Ex Officio* NCAB Members

Col. Louis F. Diehl, DoD (absent)
Dr. Kenneth Kizer, DVA (absent)
Ms. Rachel Levinson, OSTP (absent)
Dr. Alison Martin, FDA (absent)
Dr. Hugh McKinnon, EPA
Dr. Lakshmi C. Mishra, CPSC (absent)
Dr. Kenneth Olden, NIEHS (absent)
Dr. Gerald Poje, NIEHS (absent)
Dr. Christine Sofge, NIOSH
Dr. Prem Srivastava, DOE (absent)
Dr. Ralph Yodaiken, DOL

Members, Executive Committee, National Cancer Institute, NIH

Dr. Richard Klausner, Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Mr. Philip D. Amoruso, Associate Director for Extramural Administrative Management
Ms. MaryAnn Guerra, Associate Director for Intramural Administrative Management
Dr. Robert Wittes, Deputy Director for Extramural Science; Director, Division of Cancer Treatment and Diagnosis
Dr. Faye Austin, Director, Division of Cancer Biology; Chairperson, Extramural Advisory Board
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Peter Greenwald, Acting Director, Division of Cancer Prevention
Dr. Marvin Kalt, Director, Division of Extramural Activities
Dr. Edison Liu, Director, Division of Clinical Sciences
Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences
Dr. Margaret Tucker, Chairperson, Intramural Advisory Board, Board of Scientific Counselors
Dr. Edward Harlow, External Advisor, Office of Science Policy; Member, Massachusetts General Hospital
Dr. Martin Abeloff, External Advisor and Co-Chair, Clinical Sciences Subcommittee A of the NCI Intramural Board of Scientific Counselors;

Professor and Director, Johns Hopkins Oncology Center
Dr. David Livingston, External Advisor, Chairperson of the NCI Extramural Board of Scientific Advisors; Professor of Medicine, Dana-Farber Cancer Institute
Dr. Matthew Scharff, External Advisor and Co-Chair, Basic Sciences Subcommittee A of the NCI Intramural Board of Scientific Counselors; Professor, Albert Einstein College of Medicine
Dr. Alfred Knudson, External Advisor, Special Advisor to the NCI Division of Cancer Epidemiology and Genetics; Acting Director, Intramural Genetics Program; Senior Member, The Institute for Cancer Research, Fox Chase Cancer Center
Dr. Maureen O. Wilson, Executive Secretary of the President's Cancer Panel

Liaison Representatives

Dr. Margaret Foti, American Association for Cancer Research
Dr. Marc E. Lippman, American Association for Cancer Research
Dr. Robert Martuza, American Association of Neurological Surgeons
Ms. Kerrie Wilson, American Cancer Society
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists
Dr. Bernard Levin, American Gastroenterological Association
Dr. Edwin Mirand, Association of American Cancer Institutes
Dr. Robert Frelick, Association of Community Cancer Centers
Ms. Laura Lieberman, Candlelighters Childhood Cancer Foundation
Ms. Katharine Boyce, Intercultural Cancer Council
Dr. Lovell Jones, Intercultural Cancer Council
Ms. Martha Kendrick, Intercultural Cancer Council
Dr. Armin D. Weinberg, Intercultural Cancer Council
Ms. Jean Ard, Leukemia Society of America
Ms. Dorothy Lamont, National Cancer Institute of Canada
Dr. Tracy Walton, National Medical Association
Dr. Eve I. Barak, National Science Foundation
Ms. Pamela Haylock, Oncology Nursing Society
Dr. Jeffrey Norton, Society of Surgical Oncology, Inc.
Dr. Marston Linehan, Society of Urologic Oncology
Dr. Edward P. Gelmann, American Society of Clinical Oncology, Inc.
Dr. Eli Gladstein, American Society of Therapeutic Radiologists

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CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF MINUTES OF PREVIOUS MEETING

Dr. J. Michael Bishop

Dr. J. Michael Bishop called to order the 105th meeting of the National Cancer Advisory Board (NCAB), and introduced guests representing cancer education and research

associations and advocacy organizations. He welcomed members of the public and the press and invited them to submit in writing, within 10 days, any comments regarding items discussed during the meeting. A motion was requested and made to approve the minutes of the December 1997 meeting. They were approved by the Board unanimously. Dr. Bishop recognized the contributions of the following members who were completing their terms on the NCAB: Mrs. Zora Brown, Dr. Pelayo Correa, Dr. Robert Day, Ms. Barbara Gimbel, and Dr. Ellen Sigal. On behalf of the people of the United States, Dr. Alan Rabson presented each with a framed certificate of appreciation.

FUTURE BOARD MEETING DATES
Dr. J. Michael Bishop

Dr. Bishop called Board members' attention to the meeting dates listed in the agenda. Dates have been confirmed through 1999. He asked that members report conflicts with the dates listed for 2000, which are yet to be confirmed.

REPORT OF THE DEPUTY DIRECTOR, NATIONAL CANCER INSTITUTE
Dr. Alan Rabson

Dr. Alan Rabson informed the Board that Dr. Richard Klausner, Director, National Cancer Institute (NCI), was absent from the meeting because of an invitation to present a lecture in Paris, France, and to receive the Gold Medal of Paris and the Raymond Bourgine Award. Dr. Rabson reported that Dr. Klausner had represented the NCI at a meeting in the Old Executive Office Building on January 29 during which a major cancer initiative—the 21st Century Research Fund—was announced by Vice-President Albert Gore and Secretary Donna Shalala, Director, Department of Health and Human Services (DHHS). Two provisions of the proposed initiative are a historic $1.9B increase in spending for cancer research in the NIH, which will raise the level by 65 percent over 5 years, and coverage for Medicare beneficiaries participating in cancer clinical trials.
Next, Dr. Rabson announced major personnel changes, awards, and recognitions received by NCI personnel: (1) Ms. Christina Bruce was recruited as Director of NCI's Diversity in Employment Program; (2) Dr. Michael Dean, a molecular geneticist at the Frederick Cancer Research and Development Center (FCRDC) will receive the Rhodes Award at the recent meeting of the American Association for Cancer Researchers (AACR); (3) Dr. Elaine Jaffe, NCI pathologist, was elected president of the U.S. and Canadian Academy of Pathology; (4) Dr. Maria Merino, NCI chief of surgical pathology, has been elected to the Spanish Society of Pathology; (5) Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics (DCEG) was promoted to the rank of Admiral in the Commissioned Corps of the Public Health Service; (6) Dr. Alfred Knudson received the Gairdner Award for major contributions in human genetics; (7) Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences, has been invited to present the Herbert J. Block Lectureship Award at Ohio State University; and (8) Dr. Thomas Glynn, a leader in NCI's smoking and health programs, and Dr. John Bader, Chief, AIDS Antiviral Program, FCRDC, have retired.

NCI Budget. Dr. Rabson presented highlights of the FY98 appropriations legislation, which has been enacted, and the President's budget for FY99, which has been submitted to Congress. In FY98, the NIH budget increased by more than $890M, a 7.1 percent

increase over FY97, and NCI's FY98 budget is proposed at $2.547B, a 7 percent increase over FY97. Using a slide of the NCI budget by mechanism that compared the actual figures for FY97 and the estimates for FY98 and FY99, Dr. Rabson emphasized the following points. NCI plans are to increase research project grants (RPGs) as a percentage of the NCI budget in both the current and next fiscal year. The Cancer Centers line shows an increase of more than $15M in FY99, representing about 6.6 percent of the NCI budget. National Research Service Awards (NRSA) will increase significantly in FY99, reflecting the stipend increases of about 25 percent but no increase in the number of trainees, which remains at 1,628. Research and development (R&D) contracts continue to decrease as a percentage of the total budget, from 7.7 percent in FY97 to 7.2 percent in FY99. The Intramural Program line continues to decrease as a percentage of the total, from 17.3 percent in FY97 to 16.6 percent in FY98 and a projected 16 percent in FY99. The Research Management and Support (RM&S) line, which includes funding for NCI's extramural program directors and administrators, has been limited by the legislation to a 1 percent increase in FY98 and a 3 percent increase in FY99, even as the overall NCI budget increases by 9 percent. Funding for Cancer Prevention and Control remains constant at about 10 percent of the total NCI budget, consistent with the legislative requirement. Construction funds totaling about $3M will be used for repairs and improvement to FCRDC facilities. Funding for the Cooperative Groups is proposed to increase by more than $20M in FY99, about 4 percent of the NCI total, reflecting the increasing emphasis on the clinical trials program. An increase of more than $5M is proposed for Research Career Awards in 1999. The RPG competing line shows an increase of almost 25 percent in FY99 compared with FY98, due in part to a 10 percent increase in average costs for competing awards in FY99. Because the funding of R01 grants remains a major effort, the NCI is attempting to raise the payline for funding R01 grants to the 24th percentile in FY98. Dr. Rabson noted that Small Business Innovation Research (SBIR) grants continue to be funded through paylines lower than those supported by the RPG pool because NCI is mandated to award 2.5 percent of the extramural budget as SBIRs or nearly $51M in FY98. The Institute continues its efforts to improve the quality of proposals received from small businesses.

Proposed Increase in Cancer Research Funding by 2003. Dr. Rabson provided additional information on the more than 65 percent increase in cancer research funding proposed by the Administration over the next 5 years. As part of the announcement of the 21st Century Research Fund, the Vice President indicated that the NCI would receive 90 percent of the proposed increase of $1.9B for cancer research in the NIH budget by FY 2003. The other 10 percent would be distributed among other NIH Institutes, Centers, and Divisions (ICDs) that sponsor cancer research. In another expression of support for cancer research, the Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education (Senator Arlen Specter, Chair) on January 29 introduced a sense of the Senate resolution (with 7 co-sponsors) calling for a $2B (14.7%) increase for the NIH in FY99. This increase is essentially the same as that recommended by Congressman John Porter and adopted at the December consensus conference of the Federation of American Societies for Experimental Biology (FASEB).

In conclusion, Dr. Rabson called attention to the 30-year surveillance study by Dr. Fraumeni and colleagues of a cohort of children innoculated with Salk vaccine and recently published under the title "Contamination of Poliovirus Vaccines with Simian Virus 40 (SV-40) (1955–1963) and Subsequent Cancer Rates." Dr. Rabson cited this study and the subsequent leadership provided by Dr. Fraumeni and colleagues in searching for a definitive answer to the question of whether SV-40 is a significant factor in human cancer as examples of the group's ability to address public health problems, and in this case, to demonstrate an absence of risk.

REPORT OF THE DEPUTY DIRECTOR, NATIONAL CANCER INSTITUTE
Questions and Answers

Referring to the budget line for trainees, which covers stipend increases but no change in the number of trainees from 1998 to 1999, Dr. Phillip Sharp commented that an increase in the size of the training program will be needed commensurate with the anticipated 65 percent increase in NCI funding to ensure optimal numbers of future researchers. Dr. Robert Wittes, Deputy Director, Extramural Science (DDES), noted that the NCI is reevaluating the entire training program in light of the projected increase—the portion for which the NCI has discretionary authority and the portion mandated to the NIH—to address the issue of numbers and competitive stipends.

Dr. Ivor Royston asked whether the Medicare coverage for clinical trials provided for in the 21st Century Research Fund would apply only to those sponsored by the NIH. Dr. Wittes explained that NIH-sponsored cancer clinical trials are primarily those defined as NCI-sponsored by various criteria, with a few supported by other institutes that would probably be defined by similar criteria. This initiative would be a demonstration project at first, and the National Cancer Policy Board (NCPB) has been asked to advise the Secretary, DHHS, before the end of the calendar year about the advisability of expanding eligibility for Medicare coverage to include trials sponsored by other organizations. The project, therefore, could be flexible and broad, depending on the advice of the independent NCPB.

Dr. Sigal asked about NCI mechanisms for tracking economic data related to the cost of participation in clinical trials compared with standard care outside a research environment. Dr. Wittes explained that the NCI is addressing this issue via studies in two cancer centers, across the clinical trials program, and in the context of the agreement with the Department of Defense (DoD). Dr. Sigal commented that the biggest clinical trials issue to be addressed is the perception by the Office of Management and Budget (OMB), managed care organizations, and the community that participation in clinical trials is more expensive than standard care.

LESIGLATIVE UPDATE
Ms. Dorothy Foellmer

Ms. Dorothy Foellmer, Director, Office of Legislation and Congressional Activities (OLCA), reported that the process of Congressional action on the President's FY99 budget request is beginning, with hearings first in the House and later in the Senate. Dr. Shalala, Dr. Harold Varmus, Director, NIH, and Dr. Klausner are scheduled to testify in

support of the President's budget before the House Subcommittee on Labor, Health and Human Services Education and Related Agencies in early March. Ms. Foellmer noted strong support for doubling the NIH budget over the next 5 years in both Houses of Congress, with the introduction of several budget resolutions in addition to the Senate resolution mentioned earlier. She concluded by highlighting the progress of legislation of interest to the NCI and NCAB that is being tracked by the OLCA, including legislation in the areas of tobacco, genetic privacy and discrimination, health information, and research trust funds. She pointed out that one area of health information legislation has been generating concern because of the detailed level of informed consent that might be required and the potential for affecting the ability to conduct clinical and epidemiologic research.

LESIGLATIVE UPDATE
Questions and Answers

In response to Dr. Sharp's request for more information on the informed consent issue and NCI's position on this question vis-a-vis privacy of individuals, Dr. Wittes explained that movements in the whole area of privacy and confidentiality could adversely affect certain kinds of research. Therefore, the NCI regards its immediate task as educational and is working in the general NIH context of preparing a position statement of the issues for people contemplating legislation in these areas. The situation is urgent because of the number of bills before Congress and the legislation being enacted at the state level that could affect obtaining access to medical records and the shipping of medical records across state lines. In addition, the NCI is developing initiatives to establish secure one-way databases and insulate tissue and other repositories from unauthorized access.

REMARKS BY THE PRESIDENT, AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR)
Dr. Donald Coffey

Dr. Donald Coffey, Professor of Urology, Oncology, Pharmacology, and Molecular Science, Johns Hopkins University, presented an update of public policy and education initiatives of the AACR. Over the past year, the AACR has adopted a more proactive position in its public relations. Initiatives have included 24 meetings with members of Congress, a public forum in San Diego to publicize breakthroughs in various cancers that was attended by 1,000 people, collaborations with national advocacy and consumer groups, and educational and other activities in support of cancer survivors and families. Dr. Coffey noted that the AACR in all interactions with Congress supports doubling the NIH budget, promotes adoption of the NCI bypass budget, and takes strong positions on legislation in areas such as mammography screening and tobacco. Within the AACR, efforts have been made to reach out to young investigators by offering unity and leadership, outstanding research programs, education and training, and a global understanding of cancer etiology, prevention, diagnosis, and treatment. Dr. Coffey emphasized the need for strong support from the American people in the war on cancer, and he recognized the many people who have contributed time, effort, and money to the cause during his tenure in office. He acknowledged the leadership of NCI staff and the importance of NCI funding in the training and development of extramural clinical scientists. Dr. Coffey showed four slides used in AACR presentations to Congress

highlighting the magnitude of cancer mortality compared with deaths from other high-profile causes, the level of federal expenditure for NIH and NCI compared with that for other agencies, and the portion of the tax dollar allocated for cancer research. He emphasized the magnitude of communication throughout the Nation that will be needed among the leadership, patients, consumer and advocacy groups, professional organizations, and the public to take full advantage of the opportunities for major breakthroughs in clinical research that exist today. In conclusion, he commended the goals and objectives of "The March," a collaboration of national advocacy and consumer groups and the societies to focus public awareness on this task.

REPORT OF THE DEPUTY DIRECTOR, NATIONAL CANCER INSTITUTE
Questions and Answers

Dr. Sandra Millon-Underwood asked about AACR initiatives to promote education and training of future cancer researchers and about science education programs for the young students. Dr. Coffey described a few of the initiatives, which include special efforts at public forums to work with school leaders to reach high school students. In addition, the AACR works with young associates on problems associated with finding jobs and obtaining grant support, and has developed a program of fellowships. Dr. Coffey emphasized the need to continue the upward trend of the NCI payline for grant funding.

REPORT OF THE PRESIDENT'S CANCER PANEL
Dr. Harold Freeman

Dr. Harold Freeman presented a special report highlighting the achievements of the President's Cancer Panel during the 6 plus years of his tenure as Chair. The Panel was created as part of the National Cancer Program by the War on Cancer Act (now called the National Cancer Act), which was passed in 1971. The mission of the Panel is to monitor the development and execution of the National Cancer Program (NCP) and report any delays or blockages in rapid execution of the Program directly to the President. Dr. Freeman reviewed Panel activities over the past 6 years as reflected in the subjects addressed in the Panel meetings held each year. From 1991 to 1996, 27 meetings were held in 15 American cities touching on many areas: the role of poverty as a determinant of disease; the role of training; research progress against breast cancer; technology transfer; cancer in minority populations; the role of voluntary organizations in the NCP; prostate cancer; breast cancer SPOREs; cancer and the family; evaluating the NCP; cancer statistics; the role of government in the NCP; avoidable causes of cancer; lung cancer; cancer and the role of cultures of America; the human genome project; AIDS neoplasms; progress in leukemia; and the information superhighway and its meaning for cancer. In 1996, the Panel examined issues relating to fighting the war on cancer in the evolving health care system, particularly the effect on clinical research as a result of the move toward managed care. In 1997, Panel examination of concerns of special populations in the NCP included meetings on the meaning of race in science, cancer in the aging, the real impact of the reduction in cancer mortality, and the responsiveness of the Nation's health care system to the needs of special populations. Three of the four 1998 meetings will focus on issues related to quality of care, quality of life, and survivorship. Dr. Freeman noted that the Panel will coordinate its effort with the Institute

of Medicine (IOM)/National Cancer Policy Board study and with NCAB efforts on these issues.

Dr. Freeman described the Panel's view of the National Cancer Program as coinciding with the view in the Subcommittee to Evaluate the National Cancer Act Program (SENCAP) Report. The Panel sees the Program as extending from basic research, which constitutes the engine for change, to translation of that research directed toward enhancing cancer care—from discovery to universal access and application to all American people. The Panel believes that cancer occurs under human circumstances, and these social, economic, and cultural circumstances must be accounted for in attempts to remove the barriers to education about cancer as well as the diagnosis and treatment of cancer. Biomedical discoveries must always be connected to human benefit. The Panel believes that the war against cancer will require the combined efforts of the NCI, Congress, and the Executive Branch of government acting to increase the budget, and the American people acting to save their own lives.

NEW BUSINESS I
Dr. J. Michael Bishop

As a first item of business, Dr. Hugh McKinnon, Associate Director for Health, National Risk Management Research Laboratory, U.S. Environmental Protection Agency (EPA), presented an update on efforts to resolve the apparent differences in interpretation between the findings in an EPA-sponsored conference and the presentation at the previous NCAB on Trends in Childhood Cancer. A meeting was held of representatives from the NCI and from the new EPA Office of Children's Health Protection. In the extended discussion that followed a replay by Dr. Martha Linnet of the material presented to the NCAB, plans were made for increasing interactions between NCI and EPA staff to ensure coordination of efforts related to the National Cancer Program. These plans included participation by EPA staff at the annual spring announcement of Surveillance, Epidemiology, and End Results (SEER) survey data. Ongoing collaborations between the NCI and EPA on a number of studies also were reviewed.

Dr. Bishop introduced as a topic for discussion in New Business II the establishment of a sustained liaison with the Boards of Scientific Advisors (BSA) and Scientific Counselors (BSC), which were constituted as part of the NCI response to the recommendations in the Bishop-Calabresi Report.

STATUS REPORT: IMPLEMENTATION OF THE BISHOP-CACABRESI REPORT RECOMMENDATIONS
Dr. J. Michael Bishop, NCAB Members

By way of introduction, Dr. Bishop noted that the report entitled "A Review of the Intramural Program of the NCI," was filed several years ago by the *Ad Hoc* Working Group of the NCAB (co-chairs Dr. Bishop and Dr. Paul Calabresi), which had been convened at the request of Dr. Varmus. Since then, the NCAB has received two written responses along with verbal reports from Dr. Klausner of NCI actions taken in response to the recommendations. To bring NCAB action on this report to a close, Dr. Bishop asked that members review the NCI responses to each item and comment on any issue raised by the Working Group that was believed to be unanswered. Dr. Bishop indicated that the goal of the current discussion was to get NCAB concerns on the record for future

response by the NCI. In the subsequent item-by-item review of the report, the Board reached consensus that the NCI response to many of the recommendations was complete. The Working Group recommendations identified for further response are listed below. ***NCI should reconsider its current Intramural Research Program (IRP) budget to determine whether the 25 percent allocated to the IRP is appropriate.*** The NCI response indicated that this budget line has decreased steadily since FY95 to 18.1 percent of the total NCI budget in FY97 and a projected 17.7 in FY98; the overall NIH average was 11 percent. Dr. Bishop noted that the Working Group called for a continuing report to the NCAB, particularly if the NCI budget grows at an unexpected rate in relation to the growth in the number of IRP staff. Asked about a specific target for IRP budget reduction, Dr. Bishop explained that the Working Group could not arrive at an algorithm by which to set the benchmark. Dr. Calabresi added that unlike other institutes, several NCI functions are used by the NIH as a whole; moreover, the NCI has the largest operation in the Clinical Center. Dr. Kay Dickersin asked for a clarification of IRP contract costs compared with extramural research (i.e., the FCRDC contractors versus intramural NIH employees).

The Working Group endorses the recommendation of the 1992 Task Force on the IRP for the establishment of an Administrative Policy Board chaired by the Deputy Director (DDIR), NIH. It also recommends that NCI establish its own standing committee of scientists to review administrative issues and report to the DDIR, NCI. Dr. Bishop explained that the Working Group had recommended the establishment of an Administrative Policy Board to address the purported inadequate representation of working scientists in Institute administration. He expressed concern that this recommendation has not been fully addressed, based on a recent solicitation of e-mail commentary from the intramural staff of the NCI. Dr. Rabson and Ms. MaryAnn Guerra, Associate Director for Intramural Administrative Management, listed NCI actions in response, including the regular meetings of the Intramural Advisory Board (IAB), which is composed of IRP scientific staff at all levels; the IAB subcommittee for administration, whose annual report on administrative activities has been provided to the NCAB; and a recent retreat for NCI intramural principle investigators (PIs), which included a survey that will be analyzed for use by the IAB and the administrative subcommittee.

Quality Assurance in the IRP. ***1. All intramural research should be peer reviewed.*** Dr. Bishop cited this as a central concern of the Working Group. He noted that although the NCI peer review process has undergone major revision and appears to work better, anecdotal e-mail responses voice concerns that PIs continue to exercise considerable influence on the makeup of the site visit teams. He commended the NCI response in establishing the BSC as the oversight body and defining the responsibilities for the BSC and the guidelines for the site visit review process. ***5. Use of site visits has not applied sufficient vigor in the evaluation of IRP research. Thus, NCI should . . . create a process that provides rigorous scientific evaluation. Written progress reports should be submitted to extramural reviewers chosen by the DDIR, NCI, in consultation with the BSC chair.*** Dr. Bishop stated that this recommendation was not implemented. ***8. There should be a formal, uniform process for rebuttal and appeal for the IRP PIs—to be administered by the DDIR, NCI. It should not involve the PIs' supervisors.*** Dr. Bishop

explained the Working Group's concern in making the recommendation that the review process not become too authoritarian and that the process for rebuttal be as objective as possible. He noted that the NCI response appeared to make the Division Director the court of last resort. He raised for discussion or response the possibility of adding another avenue of appeal outside the investigator's immediate chain of command. ***9. Budgets for some IRP PIs are excessive; the NCI Director should consider whether investigator budgets above a predetermined amount should undergo special review.*** Dr. Bishop noted the Working Group request that the Institute address a special review to investigators whose budgets were over a certain amount. He pointed out that, although budgets are being looked at more closely, no attention appears to be addressed to the extraordinary budgets.

Stewardship Review and Tenure Policy in the IRP. Dr. Bishop noted that the Working Group's recommendations in this section reflected the concern that mentoring, career advice, and welfare of the individual investigator, particularly junior investigators, were not receiving sufficient attention. He indicated that the processes outlined in the written response did not fully address that aspect of the performance of a division, laboratory, or branch chief, and he asked for a response or other documentation in the future. Dr. Millon-Underwood concurred that no mention was made of specific programs that were in place and seconded Dr. Bishop's request. Dr. Dickersin emphasized that providing mentoring opportunities, for example, for women and minorities, required women and minorities in positions of leadership. Dr. Bishop suggested the need for recurrent reporting on progress in these area, as well as a report on recruitment. Dr. Sharp suggested that the recruitment report include curricula vitae for the entry-level people, particularly those on the tenure track. ***8. NCI should set aside approximately $3M annually for an open grants competition within the IRP.*** Dr. Bishop reported receiving an enthusiastic response from intramural investigators to this recommendation. He noted that although steps have been taken toward implementing this recommendation, more could be done to encourage initiative, independence, and lateral thinking. ***9. Establish a program for recruitment of women and minorities at all levels.*** Dr. Dickersin asked what the NCI is doing in relation to recruitment beyond the formal government-mandated programs. ***10. Develop mentoring programs for women and minority scientists in the IRP.*** Dr. Bishop expressed the view that mentoring programs were somewhat piecemeal and asked for a fuller response. In response to a question from Dr. Day, Dr. Rabson explained that the NCI is subject to the mandate for regular reporting on the distribution of employees, for example, by sex or minority status. Ms. Guerra outlined NCI actions in implementing its formal Affirmative Action Plan to ensure diversity among NCI IRP staff, and she described plans to evaluate the entire recruitment process with the goal of formalizing that also. Mrs. Brown expressed concern that NCAB reports and recommendations on this issue to date have not produced measurable results and that further measures should be considered. ***12. An ombudsperson should be appointed by the DDIR, NCI.*** Drs. Bishop and Calabresi asked for an explanation as to why an ombudsperson has not yet been appointed.

Clinical Research in the IRP. ***3. Make translational research predominant in the clinical program.*** Drs. Bishop and Calabresi asked for more information from the

Division of Clinical Sciences (DCS) about laboratory research that is translational in manner to supplement the information already received relating to protocol research. Dr. Day defined translational research as the act of bringing understandings from model systems to human disease, and he asked for more information on how the Institute organizes itself to promote the necessary interdisciplinary research, in light of the size of both the clinical and basic research programs. ***5. The IRP clinical research program should complement rather than duplicate the research programs of extramural cancer centers and NCI-sponsored clinical trials.*** Dr. Philip Schein defined translational research as the validation of the laboratory-based observation in the human species and asked what mechanisms were in place to ensure that intramural clinical programs dovetail with the basic programs and act as their conduit into the human. He also asked for information on how full cooperation and prospective planning is achieved between the IRP and extramural clinical researchers to ensure that the research is complementary and is not duplicated. He emphasized the need to focus IRP research on projects that would be difficult to perform elsewhere. Dr. Calabresi agreed that the IRP should concentrate more on Phase I and early Phase II studies. Dr. Bishop asked for a response to the reports of difficulty in getting house staff, difficulty in getting specialty consultation, and insufficient exposure to general medical oncology in the training programs on campus. ***10. NCI should augment training in clinical research in the IRP.*** Dr. Schein suggested rotating trainees for some brief period in the pharmaceutical industry for exposure to drug development in the external world. Dr. Calabresi referred to the recommendation to expand the NCI and Navy Interagency Agreement so that patients requiring inpatient care could be housed in the National Naval Medical Center. He suggested that this should be monitored because the prospect of having more exposure to common problems is better for training and will attract better NCI fellows. Dr. Calabresi asked for recruitment figures, noting that the NCI should have one of the prime programs in the Nation.

AIDS-Related Activities of the IRP. Dr. Bishop asked for a breakdown of AIDS-specific money in the Institute budget.

NCI at the Frederick Cancer Research and Development Center. Dr. Bishop deferred consideration of the FCRDC pending the report in May on the formal internal review that has been initiated by the Director, NCI, as part of the earlier response to the recommendations of the Working Group. The Board anticipates information on the progress toward implementing the Working Group's most far-reaching recommendation—that steps be taken to bring all of the working scientists at the FCRDC within the purview of the IRP.

Drug Development in the DTP. Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA), reported that the Developmental Therapeutics Program Review Group is in the process of conducting a full-scale review of the drug development program and will submit a report with recommendations to the NCI Executive Committee (EC) and to the NCAB at a future meeting. Dr. Schein commented that the NCI drug development program has been important historically and that its mission should be defined very carefully.

NCI OFFICE OF SPECIAL POPULATIONS RESEARCH
Dr. Otis Brawley

Dr. Otis Brawley, Director, presented an overview of the history, development, current projects, and future plans for the Office of Special Populations Research (OSPR). Established in 1996, the OSPR has the mission of providing leadership and coordination on research related to special populations, which include the poor, the underserved, the elderly, and various minority groups that are defined by race and ethnicity. The OSPR has the planning goals of defining scientific questions pertinent to special populations, and articulating the needs and coordinating activities for minority and special populations. The OSPR also has become the point of contact for extramural organizations. The Office is being developed to focus on the training and career development of minority scientists, science enrichment programs for high school students, and coordinating funding to historically black colleges and Hispanic-serving institutions. Dr. Brawley explained that one category of special populations research, labeled Category 1, is specifically targeted to special populations, and Category 2 research addresses an issue of great importance to these populations but with potential benefits for all Americans. An examination of 700 peer-reviewed articles on minority issues and cancer revealed that the majority were publications of Category 2 research sponsored by the NCI.

In addition to the focus on epidemiologic, clinical, and basic research, the OSPR has responsibility for coordinating outreach research. Activities include interactions with the National Black, Hispanic, and Appalachian Leadership Initiatives on Cancer. The OSPR also works with the Cancer Information Service and other communications arms of the NCI to create culturally appropriate and efficient cancer information vehicles and channels. Meetings with divisional staff are held to discuss the scope of outreach research in the NCI now and for the future. An important task is to develop the means for conveying complicated messages about health behaviors, screening, treatment, and clinical trials as accurately as possible and without distortions that could occur from oversimplification.

The OSPR defines scientific questions pertinent to special populations, then ensures that they are being addressed by the NCI, or considers how the questions can be addressed. Dr. Brawley illustrated OSPR thinking and philosophy in executing this planning and evaluation function using the data and findings from the study that compared breast cancer incidence and mortality in blacks and whites. In like manner, Dr. Brawley illustrated how the Office addresses the issue of inclusiveness in NCI-sponsored epidemiology, treatment, cancer control, and cancer prevention clinical trials. An important finding was that the minority-based institutions in the NCI Community Clinical Oncology Program (CCOP) were able to recruit 60–70 percent of their patients who were eligible for trials. One lesson from these data was that equal proportions of blacks, whites, Hispanics, Asian-Americans, and Native Americans will go on clinical trials if they are eligible and if a relationship of trust exists between the patient and doctor or hospital where they are being treated.

It was noted that the accrual of American cancer patients to treatment trials generally parallels the incidence burden of disease among these same groups (e.g., 9.4% of cancer occur in blacks and they comprise 9.6% of the clinical trials enrollment in NCI trials). However, only 2.5 percent of the Americans with cancer go on an NCI-sponsored clinical trial at this time; the percentage for all children with cancer is about 71 percent. Dr. Brawley noted that data from a number of trials in the Clinical Trials Cooperative Group Program show inclusiveness and proportionality and suggest parity. However, these data do not address the feasibility of doing subset analyses, and simple proportionality may not allow for precise subgroup analysis of differing effects in small minority groups. Dr. Brawley stated that, although the overall picture suggests proportionality in NCI-sponsored clinical trials, some hospitals in the NCI network are experiencing difficulty in accruing blacks, Hispanics, and other minorities. Through the RFA mechanism, the NCI is sponsoring regional meetings with the communities that these hospitals should be serving to discuss the barriers to providing better service. Cancer prevention and control trials, in particular, have a low accrual of blacks and Hispanics. Discussions with patients being accrued to the various types of trials indicate that people who agree to participate in cancer prevention and control trials are in a large part fairly well off financially and educationally. Participation in these trials is difficult for the poor and not a high priority for them. The NCI is attempting to make participation less burdensome. In conclusion, Dr. Brawley described an information-gathering project under way in the OSPR, which will result in a document that details the scientific questions being asked throughout the Institute and how those scientific questions relate to special populations. This document will be available in print and electronic formats.

NCI OFFICE OF SPECIAL POPULATIONS RESEARCH
Questions and Answers

Dr. Freeman noted that the President's Cancer Panel has been attempting to resolve the question of how to balance issues of equality and justice, such as those related to accruing percentages of different populations, with conducting good science. He asked how this could be addressed. Dr. Brawley emphasized the need in interpreting data to realize that disparities, for example, in survival from some cancers, are the result of social, cultural, and anthropological constructs not genetics. Dr. Freeman suggested that race is a gross variable in explaining what happens to people and, although it is important, scientists must refine this variable to identify the underlying cause, whether it be poverty, culture, or discrimination, and act to correct that disparity. Dr. Brawley emphasized the importance of continuing to collect data on the different populations but to avoid over interpreting that data once it is collected. Dr. Bishop agreed that those data not only serve medical purposes, but also they serve as reminders of the inequities suffered by these populations.

In response to Dr. Alfred Goldson's question about OSPR goals and objectives in relation to improving the survival of minorities and the poor, Dr. Brawley stated that, because the NCI's mandate for scientific investigation, the task of the OSPR is to ensure that questions of importance to special populations are being asked. If they are not, the Office works to promote research that will answer the questions through mechanisms such as the RFA or program announcement. One success has been making people aware that equal

treatment yields equal outcome and that equal treatment does not exist in the United States.

Mrs. Brown relayed offers of assistance from historically black medical colleges and other institutions in accomplishing the goal of finding better answers for cancers in black populations. From personal experience, she emphasized the importance of having access to cancer information and treatment. Dr. Millon-Underwood observed that the outcomes of the regional conferences to engage more minority and underserved populations in clinical research should receive widespread dissemination.

STATUS REPORT: DIRECTOR, CENTER FOR SCIENTIFIC REVIEW
Dr. Ellie Ehrenfeld

Dr. Ellie Ehrenfeld stated that an early effort as Director, Center for Scientific Review (CSR), was to invest in outreach activities to identify the issues of greatest concern to the broad spectrum of people involved in the biomedical research enterprise. Six high-priority areas for immediate action were identified, and work on these areas has progressed over the year. The first area related to process issues is being addressed by the application of automated electronic information technology to streamline the application process and shorten the time of review. A second major area revolved around questions about the organization of CSR study sections, and the CSR has undertaken a number of activities to address them. A panel on scientific boundaries for review has been appointed with the charge to evaluate the current division of scientific fields in CSR and to develop guidelines for the establishment of review boundaries. With the Congressionally mandated integration into the NIH of the formerly separate Institutes for mental health, drug abuse, and alcohol, the CSR now has responsibility for review in these areas. As a result, study sections for neuroscience, AIDS, and behavioral science are being reorganized. Twenty-one new study sections for neuroscience grants will begin operating in June 1998, AIDS study sections are nearing completion, and the behavioral science reorganization is expected to be completed in June 1999. A third activity to address questions related to study section organization is the establishment of extramural oversight groups to focus on the function and operation of the existing initial review groups (IRGs), which are clusters of scientifically related study sections. The first three of a projected total of six oversight groups have been or are being established in the review categories of cell and developmental function, health promotion and disease prevention, and musculoskeletal and dental science.

Dr. Ehrenfeld noted that the third priority area involves changes in the nomination, recruitment, and appointment of reviewers. The CSR is working to institute greater flexibility in the roles that reviewers are asked to play and to balance the necessary breadth of review expertise in senior leaders with the depth of technical expertise needed to review the increasingly multidisciplinary research approaches that are being taken. In all cases, legal and cultural aspects are being considered to improve the representation on review committees of the complete spectrum of the research community. Two other priority areas are being addressed by (1) the establishment of a training committee within the CSR to improve the consistency across study sections and the functioning of CSR

staff responsible for the review process; and (2) the development of mechanisms to improve CSR communication and interaction with the institutes and centers.
Dr. Ehrenfeld stated that the final priority area being addressed involves response to concerns about the review system expressed by some segments of the biomedical research community. One of these is the clinical research community, and steps taken to date include the recruitment of Dr. Michael Simmons, University of North Carolina, to work part-time as a CSR liaison to that community. Dr. Simmons is helping the Director, CSR, to address issues raised by the clinical research community and to implement recommendations made in previous studies of the status of clinical research. Although many of the problems facing this community are not related to peer review issues (such as lack of training in writing grant applications, inherent limitations on the crispness of the scientific method that can be applied to experiments with humans as subjects, and macro factors in medical school environments and society in general that discourage clinical research), there is a perceived bias against clinical research activities in study sections and among the reviewer population. Using the definition of clinical research adopted by the NIH Director's Panel on Clinical Research (the Nathan Report), the CSR is focusing on one subtype, namely, patient-oriented research, which includes the development of new technologies, mechanisms of human disease, therapeutic interventions, and clinical trials. Within that subgroup, concern is focused especially on translational research in small, single-center clinical trials and experiments. Analysis of data on the 1994 reviews showed that approximately two-thirds of the clinical research applications were reviewed in 23 study sections (referred to as high density), and the remaining third were reviewed in 50 other study sections (low density). Success rates for grants reviewed in the high-density sections were equivalent to rates for basic science grants reviewed in those sections, but rates for grants reviewed in low-density study sections were significantly lower.

With the help of Dr. Simmons, a set of proposals for changes in the CSR review of clinical research applications has been formulated, some of which will be conducted as controlled experiments with pilot runs, with subsequent evaluation. Dr. Ehrenfeld described the implementation strategies completed to date and asked for NCAB comments and input. To address the low-density review problem, cardiovascular and clinical oncology applications, which account for about one-half of the clinical applications received, will be organized into two scientific area clusters, with new special emphasis panels for the exclusive review of patient-oriented translational research and small clinical experiment research.

Another set of possible solutions has been developed to handle the remaining half of the clinical research applications, which are too diverse to be amenable to clustering. These will be piloted individually with the goal of developing creative solutions to the ever-present problem of "odd duck" applications that are received in all scientific areas. A final experiment proposed by Dr. Simmons, which is being explored in conjunction with several Institutes, is based on the timeliness and desirability of establishing a new study section for review of large, multicenter clinical trials for outcomes research and health services research.

In conclusion, Dr. Ehrenfeld discussed the need to prepare now for the future evaluation of the effectiveness of the large number of changes that are being implemented. To address this need, an Office of Evaluation has been established within the CSR, and measurable goals and objectives are being defined as part of the proposals for change.

STATUS REPORT: DIRECTOR, CENTER FOR SCIENTIFIC REVIEW

Questions and Answers

In response to Dr. Sigal's question about the disciplines envisioned for the special emphasis panels, Dr. Ehrenfeld presented an overview of how cardiovascular and clinical oncology study sections are being reorganized to ensure that appropriate reviewers are assembled for the grants to be reviewed. This reorganization includes an analysis of types of grants received repeatedly in past cycles to develop a roster of expertise from which to recruit both the permanent core for the study section and ad hoc reviewers. To perform this exercise, the Office of Extramural Research through its Peer Review Oversight Group has been evaluating the identification and coding of clinical research reviewers. A process also has been developed to code research on a scale from most basic to most clinical. In response to questions from Dr. Frederick Li and Dr. Ivor Royston, Dr. Ehrenfeld provided additional information about the variability envisioned for future study sections and how they will operate. Dr. Bishop asked if CSRs could provide advice about how the review of intramural investigators can be conducted in a more objective and critical manner and received an affirmative reply.

MINI-SYMPOSIUM: EVIDENCE-BASED MEDICINE AND THE COCHRANE COLLABORATIONS

Dr. Kay Dickersin

In her introduction, Dr. Dickersin described the status of efforts to identify the best scientific evidence on which to base the administration of medical or any health care intervention and the emergence of the evidence-based medicine movement, which, together with recent information technology advances, form the background for the Cochrane Collaboration. Dr. Dickersin noted that this international movement is well supported financially in Europe, Australia, and Canada but has not been as strong in the United States. She introduced Dr. Cynthia Mulrow, Professor of Medicine, University of Texas Health Sciences Center, and Director, Veterans Administration Cochrane Center, to present an overview of the Cochrane Collaboration; Dr. Liam O'Toole, Medical Research Council, United Kingdom, to present a U.K. funder's view of the Collaboration; and Dr. Christopher Williams, Coordinator, Cochrane Cancer Network, to report on the Cancer Network within the Cochrane Collaboration.

Systematic Reviews and Evidence-Based Medicine—Dr. Cynthia Mulrow

Dr. Mulrow outlined the rationale for systematic reviews of research evidence, which are efficient summaries that can help both clinician and investigator separate the known from the unknown in health care practice. Because they use a structured approach to identifying and reviewing the literature, they limit selection and other types of bias in summarizing and in interpreting research evidence. Dr. Mulrow noted that the Cochrane Collaboration, which has recognized the value of systematic reviews, is an international nonprofit organization whose mission is to prepare, maintain, and disseminate systematic

up-to-date reviews of health care interventions. Its aims are to produce systematic reviews that are evidence-based, easily accessible, internationally developed, quality controlled, clinically useful, and periodically updated. The team within Cochrane is currently composed of 4,000 collaborators representing 70 countries and about 600 reviewers, co-reviewers, or reviewers in training. A network of 15 Cochrane Centers throughout the world support the infrastructure of the Cochrane Collaboration, and approximately 45 collaborative groups produce the systematic reviews. The focus of the review groups is classically around the treatment of a disease or health problem, with emphasis on clinical outcomes and rigorous data. The main tangible product is the Cochrane Library, which contains a database of the already developed and regularly updated systematic reviews, a database of abstracts of reviews of effectiveness, a systematic review methodology bibliography, the Cochrane Controlled Trials Registry, and an instructional handbook. Cochrane users include clinicians in a wide range of disciplines, consumers, clinical guideline development groups, drug regulatory authorities, educational institutions, and health care insurers and funding agencies. The Cochrane Collaboration has an extensive alliance and networking relationship with many entities, including the Agency for Health Care Policy and Research (AHCPR) and the Veterans Administration in the United States. The Cochrane Library is available on CD-ROM and over the Internet. Dr. Mulrow concluded her presentation by demonstrating how to conduct online searches in two of the databases—the Controlled Trials Registry and the Database of Systematic Reviews.

U.K. Medical Research Council View on Systematic Evidence and the Cochrane Collaboration—Dr. Liam O'Toole

Dr. Liam O'Toole presented background detail on the Medical Research Council (MRC), the MRC approach to clinical trials and how systematic evidence applies, the MRC rationale for supporting the Cochrane Cancer Network, and future directions of the Network. He described the MRC as a publicly funded body whose mission is to promote and support high-quality basic, strategic, and applied research. The MRC independently decides on the research to be funded, but under a concordant with the U.K. Department of Health agrees to focus funding on areas that are of priority to the Department or that complement Department research. In return, MRC patient care costs associated with clinical research are covered by the National Health Service (NHS). With its current portfolio of 150 ongoing trials, the MRC is the largest funder of U.K. research.
Dr. O'Toole reviewed the challenges to funding clinical trials in a time of increasing numbers of questions to answer (including the large and long-term financial commitment, use of public money, responsibility to patients, and limited expertise) and described the new MRC trials procedures developed to more efficiently meet those challenges. Key elements of the new process are the call for outline proposals, using an application form structured to ensure that the question to be asked is compelling, and the full proposal stage in which MRC expertise are brought together to provide feedback to the clinicians developing the trial. Dr. O'Toole noted that Cochrane systematic reviews are particularly important to the outline stage where the threshold for acceptance is high. About 60 of the 150 MRC-funded clinical trials are for cancer, some through grants to individuals and some through the system of cooperative groups. Concern with the quality of questions being asked in the cooperative groups led to a reorganization of the group structure and

provided the impetus for MRC to consider funding the Cochrane Cancer Network. Dr. O'Toole noted that the MRC has watched developments in this area and was supportive of the aims of evidence-based medicine and the move toward more systematic handling of the evidence. The initial infrastructure of the Cochrane Collaboration was the U.K. Cochrane Center funded by the Department of Health. The MRC has been providing support for overviews in strategic areas where MRC has an existing portfolio of trials and for methodological research that underpins the overviews. The MRC also would like to support training for clinical fellows who would be funded on the basis of conducting systematic reviews, many of them within the Cochrane Collaboration. The MRC is particularly interested in the potential systematic evidence for informing clinical trial design and prioritization. The MRC provides 95 percent of the funding for the Cochrane Cancer Network, largely for coordinating the work of the review groups to ensure maximum quality reviews and minimum wasted effort. The rationale for funding the Network was based on the need to inject systematic and independent input into the process by which the cooperative groups were generating trial questions and to complement the existing MRC advisory system, particularly because of the growing need to prioritize.

Dr. O'Toole described the operation of the newly reorganized MRC clinical trials cooperative groups and the part played by the Cochrane Cancer Network in the peer review process. Responsibility for receiving and ranking outline proposals rests with the new Oncology Trials Advisory Committee, which includes a representative from the Cancer Network who provides systematic evidence on ongoing and completed cancer trials. Currently, the representative is Dr. Williams. Dr. O'Toole stated that the MRC regards the Cancer Network as a pilot for other areas toward the end of introducing independent and systematic evidence at the early stage of the peer review process. This would be done by feeding into the peer review system published results, information on current trials, and as much information as can be gathered on planned trials to inform decisions about MRC investment in future trials. Dr. O'Toole concluded that, for the pilot project to have the maximum impact on the quality of decisionmaking, an international focus is needed to collect the best information worldwide.

Evidence-Based Cancer Care: The Role of the Cochrane Cancer Network— Dr. Christopher Williams

Dr. Christopher Williams described the Cochrane Cancer Network (CCN) as an opportunity to use the entire body of evidence collected within cancer clinical trials to further the goal of making better decisions about the research of the future. He contended that systematic reviews represent the most scientific methodology for gathering evidence, but that they should be read critically and interpreted in the light of the strength of evidence that they present. The idea for systematically reviewing and maintaining reviews of evidence in clinical trials was presented by Archie Cochrane in 1970, but another 20 years elapsed before the first meeting of the Cochrane Collaboration. The CCN was registered with the Collaboration in June 1997 to facilitate the process of preparing and maintaining systematic reviews in cancer. Components of the CCN are the Cochrane Centers, the Collaborative Review Groups (CRGs), which produce the actual reviews, the Cochrane Collaboration Methods Working Groups, the Consumer Network,

and Cochrane fields, which cross many boundaries in medicine (e.g., care of the elderly). In addition to facilitating the development of CRGs, the CCN searches for trial reports, helps with the dissemination of the reviews and other materials, and promotes the cancer CRGs within and outside the Collaboration. Dr. Williams explained that the review process is driven by software called RevMan, which guides the reviewer to register the title; produce a protocol, which is peer reviewed; publish the protocol on the Cochrane Library; identify reports and abstract data; tabulate and synthesize; produce the review; publish it on the Library; and respond to comments. Dr. Williams emphasized the importance attached to the rigorous internal and external review of each product. Current CRGs cover lung, breast, colorectal, gynecological, urological, prostate, ear, nose, and throat, hepatobiliary, upper GI and skin cancers, as well as palliative therapies, supportive care, tobacco addiction, and eyes and vision. Future plans are to develop CRGs for pediatric and hematologic cancers, increase participation in current CRGs, recruit regional coordinators, establish a central secretariat to handle comments and criticisms, and recruit personnel to edit and disseminate the Cancer Library. Enhancements to the Cochrane Library are planned, with the help of funding from the European Union, the European Organization for Research into the Treatment of Cancer (EORTC), and a large patient-centered cancer charity in Europe (BACUP). These enhancements, which include a database of current randomized clinical trials, will be designed to interest consumers and promote widespread use of the database by the cancer community.

To conclude the symposium, Dr. Dickersin called attention to the material in the meeting notebook that includes the written list of questions about evidence-based medicine and suggestions about how the NCI and NCAB can become involved in the Cochrane Collaboration. She asked for comments and discussion.

MINI-SYMPOSIUM: EVIDENCE-BASED MEDICINE AND THE COCHRANE COLLABORATIONS

Question and Answer

Dr. Bishop asked whether there was evidence that the Cochrane Library was being used by practicing physicians in the community. Dr. Mulrow cited examples of training programs across the United States that are using the Cochrane Library in their informatics training sessions for both medical students and house staff, including Duke University, the University of Maryland, and the University of Texas at San Antonio. A project is under way to translate some information to make it more accessible to consumers outside academia.

Dr. Sharp asked how peer leaders are chosen for the groups that conduct the systematic reviews. Dr. Williams described the bureaucratic steps specified for organizing Cochrane review groups, which included a formal exploratory meeting, review of the proposed module by the Steering Committee of the Cochrane Collaboration, and external peer review at both the protocol review stage and the review production stage. Dr. Mulrow added that judgments made in collating the evidence have been made explicit to the reader. Dr. Day asked whether experience exists for using systematic reviews to determine coverage of health care costs. Dr. Mulrow noted that systematic review information is used by groups of people in certain managed care organizations and some pharmaceutical companies as a basis in developing their formularies. Dr. Schein cited the

complexity of analyzing clinical data and doubted that 200 reviews could be conducted in 2 years. He suggested the need for a collaborative effort to concentrate on about 15 of the most critical issues facing the field. Ms. Stovall emphasized the need by patient groups for answers regarding what is the acceptable level of evidence to support treatment decisions. Dr. Williams noted that the Cochrane Collaboration does not make such conclusions. Within the Cancer Library, the Cochrane Collaboration is working with the EORTC to have regional groups draw up some conclusions for practice in those regions, recognizing that most reviews will not provide a clear answer about best practices. Dr. Bishop asked whether the managed care sector of American medicine had shown interest in supporting this activity. Dr. Williams replied in the affirmative, but noted that the Cochrane Collaboration wants to ensure access by everyone. Dr. Li asked about quality control of the reviews. Dr. Williams noted that the Collaboration had not yet begun to implement a routine and systematic re-review of a small fraction of the studies, but random samples of reviewers' work is cross-checked. Dr. Calabresi asked if the Collaboration had reviewed the consistency of the level of critique among the various groups. Dr. Williams noted that the methodological group is addressing those questions but not enough reviews have been produced yet to fully address those issues. Quality in the reviews and in the process for producing the reviews is a constant theme and that readers can comment and distinctly influence the quality of each review. Dr. Mulrow added that editors in each collaborative review group work to improve the process and quality of review. In response to a question from Dr. Day, Dr. Williams noted that site-specific large trials such as those conducted in the U.S. clinical cooperative groups are the bedrock of most studies. He added, however, that a study of NCI-sponsored large trials showed that about 10 percent are not published and that they have a higher negativity rate than the 90 percent that are published, creating a bias to be overcome in the reviews.

IMPLEMENTATION OF PROGRAM REVIEW GROUP RECOMMENDATIONS
Dr. Robert Wittes

In his introduction, Dr. Wittes noted that, because reports of the Clinical Trials, Cancer Prevention, and Cancer Control Program Review Groups tended to overlap in their recommendations, the progress report on implementation would address those aspects in all of the reports dealing with early detection, clinical trials, and prevention. He explained that implementation groups comprised of NCI staff and extramural experts had been organized in each area, with co-chairs representing both communities.

Clinical Trials Review Implementation Committee—Dr. Michaele Christian

Dr. Michaele Christian, Associate Director, Cancer Therapy Evaluation Program, DCTD, noted that the charge to the 37-member committee was to think broadly about the design of an optimal clinical trials program, using the report of the Clinical Trials Program Review Group (CTPRG) as a starting point. The committee has structured its considerations into 13 major focus areas and plans to develop specific proposals in each of those areas and to address each recommendation of the CTPRG. These proposals will be presented to the NCAB and BSA. At its first meeting on December 5, the committee developed a common functional vision for the clinical trials program, which was to develop: (1) a system that is open and flexible enough in funding and structure to shift

priorities to pursue the best scientific opportunities and ideas and to accommodate high-risk novel ideas; (2) a system that is accessible to all; and (3) a system with measurable outcomes for determining success that can be implemented realistically within the prevailing health care system. At the second meeting, the committee reviewed ongoing NCI initiatives that address some of the major focus areas and organized two subcommittees—one to deal with accrual, access, and reimbursement issues; the other to consider idea generation, prioritization, and concept review. These subcommittees will meet separately to begin to formulate models for change. Two working groups also were formed to work with NCI staff on developing models for the peer review system and early clinical trials program. Monthly meetings of the committee as a whole are scheduled for the coming months, and a June completion date is envisioned. Specific plans to address the CTPRG recommendations for presentation to the NCAB and BSA will be made. Dr. Wittes emphasized the open nature of the implementation process and the sincere quest for innovative ideas and models from the extramural community.

Early Detection Response Implementation Committee—Dr. Barnett Kramer

Dr. Barnett Kramer, Deputy Director, Division of Cancer Prevention, explained that the early detection and screening recommendations to be addressed were taken from the reports of the Cancer Prevention and Cancer Control Program Review Groups. In preliminary meetings, recommendations from these reports were classified into the following categories to be addressed by the Early Detection Response Implementation Committee: (1) advisory processes, resources, and prioritization; (2) screening studies; and (3) molecular early detection and exposure or risk markers. Dr. Kramer noted that a series of questions have been compiled from the recommendations and will be sent as part of the information package to the full committee prior to the first meeting scheduled for March 10. Like the Clinical Trials Implementation Committee, this committee includes a broad range of expertise from the extramural community and intramural expertise from across the divisions. Monthly meetings are planned, with June as the target date for completion.

In response to a question from Dr. Ralph Yodaiken, Dr. Kramer noted that the informed consent process and the issue of confidentiality is being addressed at length by the National Action Plan on Breast Cancer (NAPBC). The NAPBC guidelines will be used as the model for consideration by the committee.

Chemoprevention Response Implementation Committee—Dr. Peter Greenwald

Dr. Peter Greenwald, Acting Director, Division of Cancer Prevention, reported that the general approach to implementation in this area will be to establish a more formal decisionmaking advisory structure for developing large trials as recommended by the Cancer Prevention Program Review Group. The Chemoprevention Response Implementation Committee has had several planning meetings, including one that was NCI-wide. Their intent is to organize the larger external advisory group on an ad hoc basis and to ask that committee to consider a model process for reviewing and recommending clinical development plans for five different agents or situations. The same committee would then be asked to critique and refine the process on the basis of results from these pilot projects before establishing the process permanently. The first

three agents chosen for this exercise are selective cyclooxygenase 2 (COX2) inhibitors, selective estrogen receptor modulators (SERMs), and selenium compounds. Dr. Greenwald presented results from epidemiological, preclinical, and early clinical studies, which formed the basis for selecting these agents as priorities. The new advisory committee will be given this information and will have the task of suggesting further steps. Agents or situations for later consideration are the retinoids/rexinoids and the implications for preventing stomach cancer in the treatment of patients who tested positive for Helicobacter pylori.

Dr. Greenwald explained that the Physician Data Query (PDQ) database and DCP's Human Intervention Studies (HINTS) computerized data system will be the major databases for chemoprevention trials. The PDQ database is currently undergoing a major redesign, and the HINTS will be modified to capture detail that goes beyond PDQ. Dr. Greenwald noted that the advice of the various Program Review and Working Groups will be used as much as possible for issues such as animal models and biomarkers to feed into the chemoprevention program. Other major questions to be addressed are (1) whether a budget for large Phase III prevention trials should be specified within which the new advisory group would have to prioritize; and (2) whether a centralized quality control laboratory for biomarkers should be established, possibly through the cooperative agreement mechanism. The concern is to ensure adequate validation of the sensitivity, specificity, and predictive value of intermediate endpoints and to ensure comparability across studies. In conclusion, Dr. Greenwald noted that the Chemoprevention Implementation Committee will categorize the recommendations into like groups and prepare a response for each area. For example, a committee on nutrition has been organized. Because these issues extend beyond the NCI, current plans are to form a group that includes representatives from the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), U.S. Department of Agriculture (USDA), and other institutes, as well as extramural scientists, to define and address some of the nutrition issues. Dr. Greenwald cited the question of whether trans-fatty acids increase the risk of breast cancer as the type of issue this group would deal with because of the health and labeling implications for their use. Another example of a nutrition issue requiring immediate attention is the engineering of foods for production purposes without an adequate basis in biomedical research.

To conclude the implementation report, Dr. Wittes noted that analogous activities in the areas of surveillance behavior and tobacco would be addressed at the May NCAB meeting. He asked for advice from Board members about the implementation process as it is evolving. Dr. Bishop commended the diversity of the committees, which include broad extramural scientific, advocacy, and consumer representation.

STATUS REPORT: DIRECTOR'S CONSUMER LIAISON GROUP
Ms. Eleanor Nealon

Ms. Eleanor Nealon, Director, Office of Liaison Activities (OLA), reported that 15 consumer advocates from diverse communities have been recruited to form the Director's Consumer Liaison Group (DCLG). The role of the DCLG is threefold: (1) help NCI increase consumer advocate representation on program and policy advisory committees

and other groups; (2) serve as a primary forum for discussing issues and concerns and exchanging viewpoints that are important to the broad development of NCI programmatic and research priorities; and (3) increase collaboration with the cancer advocacy community. In a process that began in January 1997, a planning group of NCI staff and advocate representatives helped define the initial role of the group, the criteria and categories for membership, the screening and review process for member selection, and the nomination process. Eligibility for nomination was based on the individual's involvement in the cancer experience and representation of a constituency. Nominees were evaluated by preestablished criteria for their cancer advocacy experience and their ability to communicate, think globally, contribute to the group process, and have leadership skills. Also considered in the nomination process were the desired characteristics for the DCLG as a whole to help ensure that it reflected the breadth and diversity of the consumer advocacy community. These characteristics were multicultural diversity, broad mix of cancer sites, age and geographic diversity, and representation of the medically underserved, both sexes, and a wide range of organizations. The most qualified individuals were interviewed by telephone, and a slate was drawn up from which Dr. Klausner selected the 15 members of NCI's first Director's Consumer Liaison Group. Members serve for 3-year terms and will meet 2–3 times a year. Recommendations and advice will go to the Advisory Committee to the Director for the present, but arrangements are under way to make the DCLG a chartered committee. During the nomination process, four issues of greatest concern to cancer patients today were identified by persons making nominations: (1) access to reliable understandable cancer information; (2) access to effective quality cancer treatment, including clinical trials; (3) survivorship issues, including increased rehabilitation and psychosocial support; and (4) increased involvement of the advocacy community in setting research priorities. The DCLG met for the first time in December to begin developing operating plans. Three co-chairs were selected, official liaison with the NCAB was requested, and three subcommittees were formed to reflect areas of interest: communication, informed consent issues, and genetics and tissue collection. At the meeting scheduled for April 30-May 1, the DCLG will address topics from the first agenda that continue to be of concern. Members have expressed an interest in helping with the PDQ redesign effort and with the development of the clinical trials Web page, in developing mechanisms for inviting wider input from consumers, in helping to streamline both the general informed consent document and the one for tissue collection for future research, and in helping to develop mechanisms and criteria for identifying additional consumers for NCI committees and groups. Currently, the OLA is working with DEA to identify resources for peer review study sections. Orientation and evaluation for consumers in peer review are being developed with the DEA and the Office of Cancer Communications.

STATUS REPORT: DIRECTOR'S CONSUMER LIAISON GROUP
Questions and Answers

Dr. Bishop commended the NCI for leading the way in granting consumers a role in peer review. He welcomed the opportunity for public discussion of the virtues and difficulties related to this action, which has been a controversial issue among scientists. He reported that the DCLG has been invited to be an official liaison group to the NCAB. On behalf of

the cancer survivor community, Ms. Ellen Stovall commended the work of Ms. Nealon and NCI staff involved in organizing the DCLG. Dr. Sigal solicited the help of the DCLG in communicating the importance of clinical trials as part of the effort to increase participation. Dr. Goldson asked about the mechanisms for implementing DCLG recommendations on these issues. Ms. Nealon noted that the focus in these early stages of development is to find out how the DCLG wants to operate. She suggested that issues will evolve in different ways, depending on the issue, and that the DCLG will probably play a large role in their own communities as well. She surmised that the group would be open to collaborations with other groups on issues of common interest, and she welcomed ideas from NCAB members.

NEW BUSINESS II
Dr. J. Michael Bishop
Annual Request for Applications (RFA) Report—Dr. Marvin Kalt

In response to the request for an annual report on use of the Request for Applications (RFA), Dr. Kalt gave an overview of the process, past use, and anticipated directions for the future. In FY97, seven NCI-wide RFAs were funded through the research project grant (RPG) budget line, as well as three RFAs that were co-funded with other institutes where the NCI paid at least one award. A total of 44 awards were funded in FY97 for about $16.1M (about 6 percent of the RPG pool). The success rate for the combined responses to all FY97 RFAs was under 16 percent. By comparison, the success rate overall for all non-RFA RPG awards in FY97 was 29 percent. In FY98, 15 RFAs are anticipated for which a preliminary budget of about $23M has been allocated, representing under 9 percent of the RPG pool in the competing line. Dr. Kalt reminded the Board that use of RFAs is required for cooperative agreement competitions and other large mechanisms. A number of the RFAs in the non-R01/P01 line are anticipated for career development, clinical trials, and resource areas (for example, the cancer genetics network). Whether the dollars estimated in the preliminary budget will be expended will depend on the quality of applications received and what the other needs are in all other dollar pools as this becomes clear through experience gained over the three rounds of applications. For FY99, a process will be developed for the timing and release of RFAs scheduled for the September 1998 council round as more is known about the appropriations bill for FY99. Dr. Kalt presented lists of four Board rounds of RFAs that have been announced and for which grant applications will be received for funding in FY98 and early FY99. He called attention to the emphasis in the titles on clinical research initiatives, enabling technologies needed to pursue opportunities indicated in the Bypass Budget, and career development. A substantial number of concepts will be considered by the NCI EC in coming weeks for presentation to the Board of Scientific Advisors at their March and June meetings. Concepts approved then will be the RFAs targeted for awards in FY99 and will go to the February, May, and September NCAB rounds. Dr. Kalt projected that the NCI would have a complete program of initiatives in FY99 that clearly reflect the priorities that have been agreed upon and are described in the Bypass Budget, should those not be covered under the regular unsolicited kinds of applications. Moreover, the NCI is working to improve communication with the potential applicant community as a means of providing extra time to plan applications, especially where complex consortial agreements are called for. As soon as the concepts are approved by

the BSA, they will be made known on the NCI Web site (under "what's new" on the NCI Home Page) with the recognition that not all BSA-approved concepts move forward to issuance.

Report of the Subcommittee on Cancer Centers—Dr. Robert Day

Dr. Day presented the written report of the Subcommittee on Cancer Centers for Board approval. In this first meeting since the new cancer center guidelines went into effect, the Subcommittee heard reports from NCI staff on applications received and anticipated, the budget, and the funding plan. Because of the interest in how the new guidelines are being conducted, both for applicants and reviewers, the Senior Review Administrator for cancer center grants and a representative from the review committee joined the discussion. The Subcommittee heard that the reviews and reviewers comments reflect a greater emphasis on the science in the centers, a primary recommendation of the Cancer Centers Program Review Group. The Subcommittee was also informed, on behalf of the review staff, that the reviews were going well and that the cancer centers program was in good shape.
A motion was made to approve the report of the Subcommittee on Cancer Centers. The motion was seconded and approved unanimously.

Report of the Subcommittee on Planning and Budget—Dr. Ellen Sigal

Dr. Sigal presented the written report of the Subcommittee on Planning and Budget. She briefly summarized the discussion and concluded that the committee was satisfied that the operating budget for FY98 did reflect the priorities in the FY99 Bypass Budget.

NCAB Liaison With the BSA and BSC—Dr. J. Michael Bishop

Dr. Bishop raised the issue of maintaining regular liaison between the NCAB and the BSA and BSC as recommended by the Working Group on the Intramural Program. He asked for advice from the Board on how that could be accomplished. One suggestion was to appoint two NCAB members—one scientist and one nonscientist—as liaison to each of the two groups. Dr. Day suggested that oversight of the liaison between the ERP and IRP should be a high-priority function for NCAB representatives to those bodies. Dr. Royston suggested that the NCAB representatives should be full participants of the BSA or BSC. Dr. Bishop agreed to take the suggestions under advisement and discuss them with Dr. Klausner.

As a final item of new business, the Board agreed to set aside the final 15 minutes of each meeting for an autobiographical sketch from members in the interest of becoming better acquainted with each other's professional activities. Dr. Bishop volunteered to present his report in May.

ANNUAL DELEGATIONS OF AUTHORITY
Dr. Marvin Kalt, Ms. MaryAnn Guerra

By way of introduction, Dr. Kalt explained that the NCI has extensive authorities to train scientists within the IRP and brings the appointment mechanisms to the Board for approval each year. He called attention to the document in the meeting notebooks entitled "Guidelines for National Cancer Institute Staff in Negotiating Desirable Adjustment in

Grant Amounts and Terms." By approving this document, the Board would grant Institute program staff the authority to make adjustments in the awards without the requirement for Board approval. The adjustments would be in time and amount and would represent areas within the framework of content already considered by peer review.
A motion was made to continue those authorities. The motion was seconded and approved.

Ms. Guerra reminded the Board that Section 413 of PHS Act, P.L. 103-43, mandates that the NCI Director, in carrying out the National Cancer Program, shall, in consultation with the NCAB, support appropriate programs of education and training. In that regard, she presented an overview of fellowship mechanisms in use at the present, together with a report on the number of fellows in each. The Cancer Research Training Award was established in January 1998 as the universal training program for all NCI domestic in-house fellows and as the umbrella-appointing mechanism for NCI specialized fellowships. The stipend amounts, which have been standardized for all NCI trainees, also are applied to appointments made under the NIH foreign Visiting Fellow Program. NCI specialized fellowships administered under the Cancer Research Training Award and the number of fellows in 1997 are the Cancer Epidemiology and Biostatistics Training Program (14 fellows), Cancer Genetics and Epidemiology Training Program (2), Cancer Nurse Training Program (6), Cancer Prevention Fellowship Program (19), Health Communications Internship Program (8), Technology Transfer Fellowship Program (29), and Research Scholars Program (established 5/97; open for applications until 4/24/98). Ms. Guerra presented information in response to issues raised by the NCAB. Referring to the concern expressed that the NCI was considering the termination of the nursing award in the previous year, she explained that the Clinical Center (CC) is responsible for recruiting and appointing nurses and has encompassed the Oncology Nurse Training Program within their overall training program. All nurses undergo a 6-month orientation period that includes cancer. Nurses to be assigned to oncology patient care units undergo additional training to satisfy the necessary oncology training requirements. In the past, the Clinical Center was experiencing difficulty in recruiting clinical nurses, and the NCI Cancer Nurse Training Award was established to address this need. The Clinical Center has indicated that the shortage no longer exists, so the NCI is actively considering the development of a nurse practitioner training program instead. Ms. Guerra duly noted the suggestion received from Ms. Stovall to work in collaboration with the Oncology Nursing Society on this initiative.

Another question focused on the overlap of fellowships, training methodology, and communication across divisions. Ms. Guerra explained that individual fellowships are fairly well defined for a division, so the training and rotations are sponsored by that division. The NCI, however, has begun to implement a program whereby specialized fellows receive supplemental training in a core curriculum that is open to all NCI fellows.

PROGRAM PROJECT REIVEW
Dr. Marvin Kalt

Dr. Kalt reported that the BSA had raised an issue about the methodology used to pursue program project grant (P01) review and had passed a motion suggesting that the

procedure be changed. The BSA was concerned on two counts about the current system's fairness and the potential for improving the overall process. The first count was in relation to the ability of the NCI review staff to recruit top-level senior scientists for service on the parent committee and for individual review of applications. The second issue had to do with the fidelity of transmission of information from the site visit team to the parent review committee. Dr. Kalt requested additional advice and comments from NCAB members. To inform the discussion, he reviewed the advantages and disadvantages of the current two-tier process, presented statistics on membership and number of grants reviewed for each of the three current parent subcommittees, compared the functions of the site visit and parent committees, and discussed issues to consider in evaluating the current P01 review process. Dr. Kalt noted that options for P01 review in the future include continuing the current two-tier process, returning to the process of constituting special emphasis panels (ad hoc reviewers) for all P01 reviews, or instituting a "hybrid review" process that combines features of both. The hybrid format, which was developed in discussions over the past year, would retain the idea of a chartered parent body that encompasses all the kinds of expertise but would change the way the review was conducted. A quorum for review would consist of a small number of the chartered parent body plus as many ad hoc reviewers as needed to do a site visit. Members of the chartered parent body would be convened each year for a think-tank type session to discuss global issues abstracted from the review of individual applications. Dr. Kalt noted that, if change was considered, a clear statement of outcome measures would need to be developed as a basis for evaluating the efficacy of the change. He asked the Board to consider whether there is a need for change at this time and, if not, what signals in the future would suggest the possibility that change was necessary or beneficial.
Following a brief discussion, NCAB members reached a consensus to reaffirm the current process for program project review.

ADJOURNMENT
Dr. J. Michael Bishop

There being no further business, the 105th meeting of the National Cancer Advisory Board was adjourned at 11:50 a.m. on Wednesday, February 4, 1998.