DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

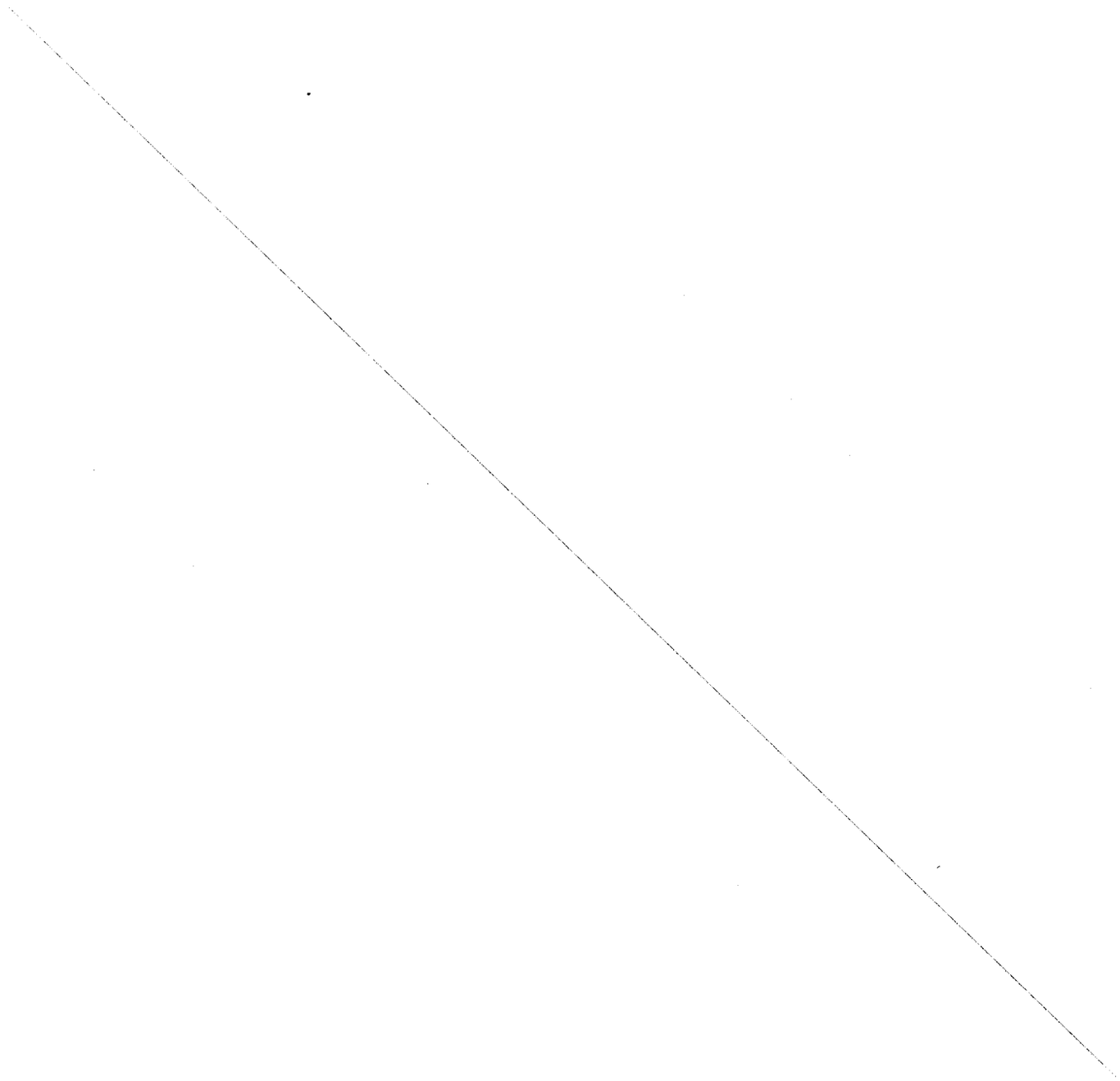
NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
September 18-19, 1989

Building 31, Conference Room 6
National Institutes of Health
Bethesda, Maryland



**Department of Health and Human Services**
**Public Health Service**
**National Institutes of Health**
**National Cancer Institute**
**National Cancer Advisory Board**

**Summary of Meeting***
**September 18-19, 1989**

The National Cancer Advisory Board (NCAB) reconvened for its 71st regular meeting at 8:30 a.m., September 18, 1989, in Building 31, 6th Floor, Conference Room 6, National Institutes of Health (NIH). Dr. David Korn, Chairman, presided.

**NCAB Members**

Dr. Erwin P. Bettinghaus
Dr. Roswell K. Boutwell
Dr. David G. Bragg
Mrs. Nancy G. Brinker
Mrs. Helene G. Brown (Absent)
Dr. John R. Durant
Dr. Gertrude B. Elion
Dr. Bernard Fisher
Dr. Phillip Frost (Absent)
Dr. David Korn
Dr. Walter Lawrence, Jr.
Dr. Enrico Mihich
Mrs. Irene S. Pollin (Absent)
Dr. Louise C. Strong
Dr. Howard M. Temin
Dr. Samuel A. Wells

**President's Cancer Panel**

Dr. Armand Hammer
Dr. William P. Longmire (Absent)
Dr. John A. Montgomery (Absent)

***Ex Officio* Members**

Dr. Allan Bromley (OSTP) (Absent)
Dr. Dorothy Canter, NIEHS
Dr. William Farland, EPA (Absent)
Captain Bimal Ghosh, DOD
Dr. John R. Johnson, FDA
Dr. Ted Lorei, VA
Dr. Lakshmi Mishra, CPSC
Dr. William F. Raub, NIH
Mr. James S. Robertson, DOE
Dr. Louis W. Sullivan, DHHS (Absent)
Mr. William D. Wagner, NIOSH
Dr. Ralph Yodaiken, DOL

**Members, Executive Committee, National Cancer Institute, NIH**

Dr. Samuel Broder, Director, National Cancer Institute
Dr. Maryann Roper, Deputy Director, National Cancer Institute
Dr. Richard H. Adamson, Director, Division of Cancer Etiology
Mr. Philip D. Amoruso, Associate Director for Administrative Management
Mrs. Barbara S. Bynum, Director, Division of Extramural Activities
Dr. Bruce A. Chabner, Director, Division of Cancer Treatment
Dr. Peter Greenwald, Director, Division of Cancer Prevention and Control
Dr. Werner Kirsten, Associate Director, Frederick Cancer Research Facility
Dr. Alan S. Rabson, Director, Division of Cancer Biology and Diagnosis
Executive Secretary, Ms. Iris Schneider, Assistant Director for Program Operations and Planning

*For the record, it is noted that members absented themselves from the meeting when discussing applications (a) from their respective institutions or (b) in which conflict of interest might occur. The procedure does not apply to *en bloc* actions.

**Liaison Representatives**

**Ms. Delores Esparza,** President, Oncology Nursing Society, representing the Oncology Nursing Society.

**Dr. Walter Faggett,** Speaker of the House of Delegates, National Medical Association, representing the National Medical Association.

**Dr. Robert N. Frelick,** Past President, Association of Community Cancer Centers, Wilmington, Delaware, representing the Association of Community Cancer Centers.

**Dr. Ed Gelmann,** Georgetown University, Washington, D.C., representing the American Society of Clinical Oncology.

**Dr. Marianna Hankert,** Program Director for Cell Biology, National Science Foundation, Washington, D.C., representing the National Science Foundation.

**Dr. Thomas J. King,** Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, D.C., representing the American Association for Cancer Research, Inc.

**Dr. Edwin A. Mirand,** Associate Institute Director and Dean of the Roswell Park Memorial Institute Graduate Division, Buffalo, New York, representing the Association of American Cancer Institutes.

**Dr. Robert Parks** for Dr. Clarence Ehrlich, President, Society of Gynecologic Oncologists, Chicago, Illinois, representing the Society of Gynecologic Oncologists.

**Dr. John F. Potter,** Director, Lombardi Cancer Center, Georgetown University, Washington, D.C., representing the American College of Surgeons.

**Ms. Yvonne Soghomonian,** Associate Director, the Candlelighter's Childhood Cancer Foundation, Washington, D.C., representing the Candlelighter's Childhood Cancer Foundation.

In addition to NCI staff members, meeting participants, and guests, a total of 24 registered members of the public attended the meeting.

## I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF MAY 15-16, 1989, NCAB MEETING MINUTES--DR. DAVID KORN

Dr. Korn, Chairman, called the 71st meeting of the National Cancer Advisory Board (NCAB) to order and welcomed Board members, the President's Cancer Panel, liaison representatives, guests, staff of the National Cancer Institute (NCI), and members of the public. He invited members of the public who wished to express their views on any part of the meeting to do so by writing to Mrs. Barbara Bynum, Director, Division of Extramural Activities (DEA), within 10 days of the meeting.

Approval of the May minutes was postponed until the following day's session.

## II. FUTURE MEETING DATES

Dr. Korn called Board members' attention to the following confirmed meeting dates: December 4-5, 1989; January 29-30, 1990; May 14-15, 1990; October 1-2, 1990; and December 3-4, 1990. Dates for 1991 to be reviewed and confirmed were February 4-6, May 13-15, September 23-25, and November 25-27. Dr. Korn pointed out that although the meeting dates for 1991 continue to be listed as 3-day meetings, the intent was to continue the 2-day meeting format unless it was necessary to do otherwise.

## III. REPORT OF THE PRESIDENT'S CANCER PANEL--DR. ARMAND HAMMER

To begin the Panel report, Dr. Hammer announced the schedule for the last two meetings in 1989 of the President's Cancer Panel. On October 13, the Panel will meet at the Stanford University School of Medicine to consider the topics of training needs and technology transfer, areas of great importance to the continued vitality of the National Cancer Program. As has been the custom in recent years, the final meeting on December 11 will be held at the NCI. Dr. Hammer explained that this meeting at NCI gives the Panel an opportunity to hear directly from the various NCI Division Directors and staff concerning their programs, problems, and priorities.

Dr. Hammer reported that the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS (Lasagna Committee) has been meeting regularly throughout the year and continues to make progress. He said that a concern had been raised in the course of committee deliberations that the drug evaluation and approval process is slowed by private insurer and Health Care Financing Administration (HCFA) policies that deny reimbursement for investigational cancer and AIDS therapies. Responding to this concern, Dr. Lasagna and his committee are submitting a proposal to HCFA requesting consideration of a new method for insurance companies to use in establishing criteria for reimbursement decisions for investigational therapies.

Dr. Hammer noted that senior staff of the NCI and Food and Drug Administration (FDA) now meet monthly to consider new drug evaluation issues, with the goal of expediting approval. He reported that on September 13, the Lasagna Committee met at the FDA at the invitation of Dr. Frank Young, Commissioner, FDA. At this meeting Dr. Daniel Hoth, Director, Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), discussed the proposed "parallel track" strategy to make available to AIDS patients experimental drugs normally available only to those on officially sanctioned clinical trials.

Dr. Hammer reported that the Lasagna Committee has unanimously agreed on a statement in response to the *Federal Register* announcement of rules proposed by HCFA regarding coverage decisions that affect Medicare reimbursements. Dr. Hammer indicated that as Chairman of the Panel, he supports the conclusions of the Lasagna Committee, which he presented to the Board, and would join in transmitting the statement to the Secretary, Department of Health and Human Services, and the Acting Administrator of HCFA. Dr. Hammer then commended committee members on behalf of the Panel for their hard work and dedication throughout the year.

Dr. Hammer informed the Board that as recommended at the previous Panel meeting at Meharry Medical College in Nashville, Tennessee, NCI continues to place additional emphasis on cancer diagnosis, treatment, and prevention in minority populations. He pointed out that Congress has attached considerable importance to the issue as evidenced by the recent House Appropriations Subcommittee directive to NCI to redouble efforts to reverse the trend of increasing cancer incidence rates among minorities and to increase support for research into the disparity in cancer deaths for persons over age 65, minorities, the disadvantaged, and the rural poor.

Finally, Dr. Hammer reported that through the Stop Cancer Project, two contributions had been made to the NCI Gift Fund: $158,000 was donated by Leonard Abramson to be directed to basic research in breast cancer, and $250,000 was donated by Lawrence and Selma Rubin for the support of research activities, particularly the development of biologic treatments for cancer.

## IV. NCI DIRECTOR'S REPORT--DR. SAMUEL BRODER

Dr. Broder began by discussing staff changes, noting the following appointments: Dr. Maryann Roper as the Deputy Director of the NCI; Dr. Michelle Evans as Special Assistant for Minority Affairs; Dr. Kenneth Paull as Chief of the Information Technology Branch, Division of Cancer Treatment (DCT); Dr. Michael Friedman as Associate Director of the Cancer Therapy Evaluation Program, DCT; Dr. Edward Sondik as Acting Deputy Director in the Division of Cancer Prevention and Control (DCPC); Dr. Richard Costlow as Acting Associate Director for the Cancer Prevention Research Program, DCPC; Dr. Brenda Edwards as Acting Associate Director of the Surveillance Program, DCPC; Dr. Claudia Baquet as Associate Director of the Cancer Control Science Program, DCPC; and Dr. Ben Hankey as Chief of the Cancer Statistics Branch, DCPC. Staff leaving the Institute include Dr. Lucius Sinks, Chief of the Cancer Centers Branch; Dr. David Joftes, Chief of the Contracts Review Branch of the DEA; and Mr. Paul Davignon, Chief of the Pharmaceutical Resources Branch, DCT.

Dr. Broder also identified several current and former NCI staff members who received significant awards or special honors: Dr. Richard Adamson, Director, Division of Cancer Etiology (DCE), received the 1989 Presidential Meritorious Executive Rank Award; Dr. Louise Brinton, Chief of the Environmental Studies Section of the Environmental Epidemiology Branch, DCE, was named President-Elect of the Society of Epidemiologic Research; Dr. Donald Fox, Chief of the Research Facilities Branch in the Centers and Community Oncology Program, DCPC, received a Public Health Service (PHS) Outstanding Service Medal; Dr. Lance Liotta, Chief of the Laboratory of Pathology in the Division of Cancer Biology and Diagnosis (DCBD), will share the Joseph Steiner Cancer Prize for his research on metastasis; Dr. Jane Henney, formerly the NCI Deputy Director, was named Chancellor for Health Programs and Policy at the Kansas Medical Center; Dr. David Korn and Dr. Robert Gallo were named to the Institute of Medicine; Dr. Michael Hawkins, Chief of the Investigational Drug Branch, DCT, will receive the NIH Equal Opportunity Award; Dr. Joost Oppenheim, Chief of the Laboratory of Molecular Immunoregulation, DCT, received the Pharma Medica Lecture Award for 1989 from the Danish

Society of Dermatology; Dr. Stuart Aaronson, Chief of the Laboratory of Cellular and Molecular Biology, DCE, received the PHS Distinguished Service Medal; Dr. Peter Howley, Chief of the Laboratory of Tumor Virus Biology, DCE, received the PHS Meritorious Service Medal; Dr. Frederick T. Li, Head of the Clinical Studies Section in the Clinical Epidemiology Branch, DCE, also received the PHS Meritorious Service Medal; and Dr. Joseph Fraumeni, Associate Director of the Epidemiology and Biostatistics Program, DCE, received the 1989 Gorgas Medal from the Association of Military Surgeons for distinguished work in preventive medicine. Dr. Broder stated that these honors and awards are recognition of the fact that NCI's most important resource is its staff, and he offered congratulations to all those honored.

In turning to discussion of administrative matters, Dr. Broder said that consistent with the advice received, the Cancer Centers Branch, along with the Training and Construction Branches, will move from DCPC to DCBD. The name of the Division will be changed to reflect its new structure, which also includes the Organ Systems Program. Five full time equivalent (FTE) staff members will be added to the Centers Branch to ensure the effective administration of the Cancer Centers Program. The DCBD Board of Scientific Counselors will also be expanded to reflect the Division's new responsibilities. A working group of representatives from DCPC, DCE, and DCT and Dr. Roper will also provide advice to the Cancer Centers Program. Dr. Roper will continue to lead the 5-year planning group and work with the ad hoc consultants representing cancer center directors. Dr. Broder expressed his view that this change makes optimal use of available resources, and he emphasized NCI's commitment to a vigorous, independent, and diverse Cancer Centers Program. He also stressed his personal interest in the program and his intention to remain involved in planning, policy, budget, and implementation issues.

Dr. Broder noted that Dr. John Durant, Chairman of the NCAB Subcommittee on Cancer Centers, would discuss a proposed additional criterion for comprehensiveness of cancer centers. He described the new criterion as specifically addressing issues of community service and outreach and as responsive to the language of the 1988 reauthorization of the National Cancer Act and the intent of Congress repeatedly expressed over the history of the Cancer Centers Program. Dr. Broder said the criterion puts into action NCI's strong commitment to transfer technologies to the community and make advances available to all Americans, especially those groups with disproportionately high cancer incidence and mortality.

New guidelines for cancer centers will be drafted and circulated to the Board for review. Dr. Broder stressed that the guidelines are not meant to be punitive, and institutions could still be funded as clinical centers even if they fail to get a comprehensive designation. There will be a 2-year transition period during which centers that recently have had their grants renewed will be able to receive an administrative designation as a comprehensive cancer center. This designation could be made by the NCI Director after consultation with the chairman of the Center Core Support Grant Review Committee and the NCAB. After this period, designation of comprehensiveness will occur as part of the peer-review process. Centers that are currently designated comprehensive would have to document that they meet the new criteria at the time of their reapplication.

Dr. Broder next announced that the combination of levamisole and 5-FU to treat Dukes' C colon cancer has been shown to reduce both the risks of tumor recurrence and death by about one-third. These results confirm the findings of an initial trial and demonstrate the value and importance of the controlled trial methodology. Dr. Broder acknowledged the efforts of investigators at the North Central Cancer Treatment Group and the Mayo Clinic, as well as staff of the Cancer Therapy Evaluation Program (CTEP) and the FDA for obtaining Group C approval status for levamisole. As a result of these findings, NCI-sponsored studies for colon cancer will

no longer have an observation-only arm. Patients randomized to untreated control arms in NCI-sponsored trials are being informed that they may benefit from the adjuvant treatment. It is likely that a clinical alert will be issued. Dr. Broder urged that patients with Dukes' C colon cancer who cannot enter a clinical trial be informed of the levamisole-5-FU treatment option. Physicians and surgeons can obtain levamisole through CTEP.

As a related issue, Dr. Broder noted that Dr. Greenwald would present the results of a study showing that dietary intervention can, in certain situations, cause polyps, the precursor lesions to colon cancer, to regress.

Turning to the smoking problem, Dr. Broder stated that DCPC, in cooperation with the American Cancer Society (ACS), was about to initiate the ASSIST program, the world's largest demonstration project for tobacco control and health promotion. The program's objective is to reduce the smoking behavior in adult men and women in 20 sites to 45 percent of the 1985 level in 5 years. Adolescents and heavy smokers are targeted as well. NCI will spend about $150 million over about 10 years on the program, and ACS will contribute several million dollars, educational materials, and the efforts of its thousands of volunteers.

In its continuing effort to address cancer in minorities as a high priority, Dr. Broder reported that an RFA for minority-based community clinical oncology programs had been released with responses due in October and awards scheduled for June 1, 1990. A total of $1.2 million per year is available to fund eight programs. To be eligible, institutions must have greater than 50 percent of new cancer patients from minority or underserved populations for participation in NCI clinical trials.

Dr. Broder also announced that the regional chairpersons and newly hired regional coordinators for the National Black Leadership Initiative on Cancer had met for orientation and training sessions.

To launch a new mammography awareness campaign, NCI and the Susan Komen Foundation will cosponsor the Women's Leadership Summit on Mammography on September 20. Dr. Broder credited Board member Mrs. Nancy Brinker with originating the idea and said that Mrs. Brinker and Nina Hyde, fashion editor of the *Washington Post*, would co-chair the event. First Lady Barbara Bush will speak at the luncheon, and Dr. Louis Sullivan, Secretary of the Department of Health and Human Services, has lent his support. Dr. Broder pointed out that an estimated 142,000 new cases of breast cancer are expected to be diagnosed in 1989, with perhaps 43,000 women dying of the disease. If women follow the current mammography screening guidelines, breast cancer deaths would decline by at least 30 percent. Dr. Broder underscored that solving the breast cancer problem required a comprehensive approach, including basic research, clinical trials, and appropriate diagnostic and therapeutic technologies.

Summarizing some legislative issues, Dr. Broder said that hearings had been held on the Federal Technology Transfer Act, and Congress had expressed enthusiastic support. He stated his view that the Act is among the most important tools available to the NCI and NIH for transferring technologies and ensuring that interactions between Government and the private sector occur. NIH has collected $3.9 million in royalties under the Act, but in general, Government agencies are hampered by a shortage of the legal expertise needed to develop agreements with industry and obtain patents.

Dr. Broder said that the first competitive renewal for the NCI Outstanding Investigator Grants (OIG) would occur in 1990. Although the awards are for 7 years, awardees are asked to

apply for renewal at the fifth year so that they can apply for an appropriate R01 or P01 grant if the OIG application should not receive a fundable priority score. Applicants will be asked to submit evidence of productivity during their initial grant period and to provide information on proposed research. Peer review of applications will be conducted by mail.

Dr. Broder also noted changes in procedures for funding conference grants. Applications will have three receipt dates a year (February 1, June 1, and October 1) rather than being accepted and reviewed on a continuous basis. This will allow better decision making about allocating conference grant funds.

As part of NCI's cancer surveillance activity and in response to a congressional mandate, NCI will sponsor a meeting on issues related to research addressing various aspects of patterns of care. Dr. Broder said this initiative also responded to the February 1989 GAO Report on Breast Cancer. A panel of experts will meet on November 7-8 to draft a report summarizing current sources of data, methodologic issues, and recommendations for conducting such research.

Next, Dr. Broder announced with pleasure that NCI has adopted McKinley High School, a technology-oriented inner city school in the District of Columbia. NCI staff will contribute to seminars and science club activities, and surplus laboratory equipment will be donated to the school. Other activities will be undertaken to advance the cause of science in the school, encourage minority students to choose science careers, and increase awareness of health issues.

In turning to the budget, Dr. Broder stated that NCI's FY88 obligations were approximately $1.468 billion, the 1989 estimate is $1.570 billion, and the President's 1990 budget is $1.646 billion. The House markup of the President's 1990 budget is $1.652 billion, and the Senate version is $1.668 billion. Dr. Broder pointed out that NCI's 1991 bypass budget is $2.4 billion.

With respect to the FY89 budget, Dr. Broder reported that Congress had approved a reprogramming of funds to cover the increased stipends for National Research Service Awards (NRSA). Approximately $1 million was redirected from research project grants and $200,000 from contracts for an approximate 90 additional trainees, bringing NCI's total number of trainees in FY89 to 1,383, 73 fewer than in FY88.

In the FY90 budget, Dr. Broder noted that the House markup includes the following earmarked funds: $1.5 million for planning a proton beam therapy center, $3 million for additional NRSA trainees, $2 million for salary costs for the restoration of FTEs previously eliminated in the President's budget, and $34 million to the Office of the Director, NIH, for a supercomputer upgrade. The Senate version restores NRSA trainees to about the 1988 level, increases funds for cancer centers to ensure that the number remains constant in FY90, directs a 5 percent increase for cancer information dissemination, specifies expanded research related to retroviruses and domestic animals and pediatric AIDS, includes $500,000 for an improved statistical series on cancer in rural areas, and provides $12.5 million in matching funds for the private money raised by the Stop Cancer program to be awarded through normal peer review for research on cancer biology and adoptive cellular therapy. The Senate version reduces the overall NIH budget by $4 million for procurement reform activities, and the NCI budget would be reduced proportionately. The Senate also provides $18 million to the NIH Office of the Director to fund specific extramural construction projects, including $2 million to the University of Colorado Cancer Center. No peer review would be involved in awarding these funds. Dr. Broder also pointed out that deficit reduction activities mandated under the Gramm-Rudman-Hollings legislation could result in an automatic 5.3 percent reduction in the non-Defense portion of the FY90 budget.

In conclusion, Dr. Broder stated that the FY91 bypass budget, which had recently been provided to the Board, had been sent to the Office of Management and Budget (OMB). The 1991 President's budget is being developed and will be made public when the President submits the budget to Congress in January.

In response to questions raised by Board members about the cancer centers, the following clarifications were made:

- An institution can be funded as a cancer center without being designated comprehensive, but the designation of a comprehensive cancer center should go only to NCI-funded centers.

- Work is in progress to develop a mark or logo that could be copyrighted and used only by NCI-designated comprehensive cancer centers.

- It is likely that centers currently designated comprehensive will meet the new criteria for comprehensiveness, but the 2-year transition period will provide an opportunity for these centers to consider whether to request comprehensive designation through the peer-review process.

- Actions will be taken, including consideration of earmarking funds for comprehensive centers, to ensure the continued existence of a certain number of such centers.

- Under the new guidelines, centers that currently are comprehensive either will have to request an administrative designation of comprehensiveness or request that designation at the time they apply for renewal of their grants.

Several Board members expressed concern about the Congressional earmarking of funds in NCI's budget for allocation to specific institutions outside the peer-review process. Although it was noted that the University of Colorado facilities project had been peer reviewed, the Board agreed to send a letter to Congress objecting to the funding of construction outside the NCI peer-reviewed construction program. It was also agreed to send a letter to Senator Frank Lautenberg commending his efforts to ban smoking on all domestic airline flights.

Dr. Enrico Mihich called attention to the consequences of the lack of appropriate consideration to the bypass budget and the increasing discrepancy between the actual budget and the bypass. He suggested that the President's Cancer Panel might consider this issue.

## V. GENE TRANSFER EXPERIMENTS IN MAN--DR. STEVEN ROSENBERG

Dr. Rosenberg stated that he would present a brief update on DCT's efforts to initiate gene transfer protocols in humans within the context of ongoing efforts to develop biologic therapies for the treatment of cancer to join surgery, radiation, and chemotherapy as cancer treatment. He defined biologic therapy as cancer treatment that acts primarily through natural host defense mechanisms as opposed to the application of external forces, such as the scalpel, radiation, or drugs, or by the administration of natural mammalian substances.

Dr. Rosenberg noted that biologic therapy was first described in 1985 and involved the use of high-dose interleukin-2 (IL-2) with lymphokine-activated killer (LAK) cells, a kind of cell that could be produced from the peripheral blood of cancer patients. Since then, more than 700 patients (80 percent with metastatic melanoma and renal cell cancers) have been treated with

high-dose IL-2-based regimens. These IL-2-based immunotherapies caused a complete regression of metastatic cancer in about 10 percent of patients and a 50 percent regression in about 33 percent of the patients.

The second generation of biologic therapy, based on the use of tumor-infiltrating lymphocytes (TILs), resulted from efforts to find a more potent cell for use in adoptive immunotherapy. Dr. Rosenberg explained that TILs are lymphoid cells that infiltrate into solid tumors and can be grown by culturing single-cell suspensions from tumors in IL-2 and that they were found to be 50 to 100 times more potent in animal experiments than LAK cells. He said that first results in 20 melanoma patients treated with this approach were reported in the *New England Journal of Medicine* as follows: 60 percent of previously untreated patients had objective responses and 40 percent of patients who had failed prior IL-2 therapy responded. More than 60 patients with melanoma have now been treated with TILs with similar results; further, 7 of 9 patients who failed treatment with high-dose IL-2 responded to TIL therapy, indicating the greater potency of TILs. To illustrate an important biologic point about this therapy, Dr. Rosenberg summarized results of treatment of a 46-year-old patient, who had widespread metastatic melanoma at about 40 subcutaneous sites. The TILs labeled with indium-111 were found to be capable of trafficking to tumor, mediating the disappearance of lesions on the posterior skull, thigh, and anterior chest wall, and causing a marked regression of very large lesions at the base of both lungs.

Dr. Rosenberg reported that the third generation of biologic therapies came about through his collaboration with Dr. Michael Blaze of NCI, and Dr. French Anderson of the National Heart, Lung, and Blood Institute (NHLBI) to modify TILs to make them more effective in the treatment of cancer patients. He explained that gene transfer is a proposed therapeutic technique in which a functioning gene is inserted into the somatic cells of a patient, either to correct an inborn genetic error or to provide a new function to the cell. He noted that researchers had formerly been limited to the isolation of lymphocytes from cancer patients and expanding them outside of the body, but modern engineering techniques have provided the opportunity to insert new genetic material (from either other humans or other species) into natural human cells to alter their properties.

Dr. Rosenberg stated that the only efficient technique for introducing new genetic material into mammalian cells involves the use of retroviral gene transduction. With this technique, retroviruses can be introduced into 10 to 30 percent of the cells being treated. The genetic material of interest, e.g., a gene coding for neomycin resistance, is introduced into a genetically crippled N2 provirus, which cannot replicate (i.e., all of the viral coding sequences have been removed). The virus thus becomes a delivery system for introducing the gene into the TIL but cannot itself replicate and infect other cells. Dr. Rosenberg explained that in this transduction protocol, the retroviral vector containing the gene of interest is mixed with the TILs in a test tube, the gene is introduced into these TILs and the virus dies without replicating, the TILs are expanded, and the resulting gene-modified cells are introduced into patients with cancer in an attempt to mediate anticancer responses.

Dr. Rosenberg noted that the initial clinical protocol involved the insertion of a gene that codes for resistance to an antibiotic, neomycin, so that studies could be performed of the long-term distribution and survival of TILs in humans. He stressed that no foreign genes had been introduced into humans; rather, the protocol was designed to study the efficacy and safety of this approach as well as to provide biologic information about this cancer treatment. He added that the goal of the present investigations is to insert genes into TILs to improve their efficacy, and that the initial emphasis has been on tumor necrosis factor (TNF).

Dr. Rosenberg described the rigorous NIH review process required for this clinical protocol. He listed the 16 different review bodies, including the Institutional Review Boards in the NCI and NHLBI Clinical Research Committees, NIH Biosafety Committee, and Gene Therapy Subcommittee of the Recombinant DNA Advisory Committee (RAC), and noted that approval was granted by the Director of NIH on January 30, 1989. A subsequent lawsuit claiming that the protocol had not undergone sufficient review was settled within a month, and implementation of the protocol was able to proceed.

Dr. Rosenberg stated that he and his colleagues were required to demonstrate to each of the review bodies that: (1) the marker gene could be inserted and get expressed in human TILs, (2) the marker gene did not significantly alter the TIL into which it was inserted, (3) detection of the marked cells could be accomplished in animal models, and (4) the procedure presented very low risk to the patient and no risk to the public. Upon satisfactory completion of this review, according to Dr. Rosenberg, the Recombinant DNA Advisory Committee granted permission to treat 10 patients (with life expectancies of up to three months) and return to the committee with more information.

Dr. Rosenberg noted that TIL therapy involves the isolation of a tumor from a patient, preparation of a single-cell suspension, and growth of the cells outside of the body until a sufficient number of cells can be harvested and returned to the patient along with IL-2 (usually about a month later). For the modified protocol, between day 15 and 20, the retrovirus is introduced into an aliquot of the culture, which introduces the gene into the cells; the gene-modified cells are grown in parallel with the unmodified cells, and both are returned to the patient. Dr. Rosenberg reported that five patients, ages 26 to 52, have been treated with gene-modified therapy since May 1989; all had advanced metastatic melanoma with very limited life expectancies. Tumor specimens were harvested from a variety of either subcutaneous or lymph node sites under local anesthesia, and evaluable sites of disease were widespread (e.g., liver, spleen, lymph nodes, subcutaneous tissue). For each patient, the transduced cells were tested for the presence of the new gene, using the Southern blot, before transfer to the patient.

Dr. Rosenberg noted that the critical feature of this protocol was to determine whether gene-modified cells would survive and distribute in the cancer patient. He said two very sensitive techniques were used to detect the gene-transduced cells in the patient: (1) polymerase chain reaction (PCR) and (2) growth of cells taken from the patient in medium containing the neomycin analog G418. He reported that for the first time, it has been possible to isolate the gene-transferred cells from patients out to almost 3 weeks in both peripheral blood and tumor lymphocytes, indicating that gene-transduced cells can survive. In addition, he said that the 24-year-old advanced melanoma patient who was the subject of this first finding had a dramatic response to treatment which was characterized by shrinkage of multiple subcutaneous lesions. He added that this patient was about to begin a second course of treatment. Dr. Rosenberg said that of the 5 patients treated, none had experienced any side effects and all had tolerated the therapy well. In safety testing requested by the FDA (i.e., checks of viral supernatant, the transduced cells, and patient serum and tumor samples), no virus was detected in the TILs, nor was there any evidence of virus in the patients.

Dr. Rosenberg continued that the goal of the next protocol is to introduce genes for substances that can improve therapeutic effectiveness. To that end, he said a collaborative effort with Dr. Mike Creegler at Cetus Corporation had resulted in the successful use of retroviral vectors to introduce the gene for TNF into patient TIL cultures. Using PCR techniques, it was possible to show that the transduced TILs and not the control TILs contained the new cytokine

gene for TNF and, in fact, had an increased production of TNF that was secreted into the supernatant. Approval to use this second generation protocol in patients has been requested.

Citing implications of these findings, Dr. Rosenberg suggested that lymphocytes may provide an ideal vehicle for the introduction into humans of genes that are useful for developing therapies for cancer as well as other diseases (e.g., bone marrow reconstitution and introduction of factor VIII into a lymphocyte to treat hemophiliac patients). In addition, there is the possibility that these modified TILs are able to induce regression of cancer in some patients (e.g., melanoma patients) and may improve the therapeutic efficacy, generally, of biologic therapy approaches.

In response to questions, Dr. Rosenberg provided the following additional information:

- The cells have been shown to express the neomycin-resistance gene that codes for the enzyme that degrades the G418, and Southern blot testing is in progress to show that the cells are, in fact, resistant.

- Quantitation with indium-111-labeled cells has been performed only to 1 week beyond therapy and as many as 10 percent of the transferred TILs have been identified in tumors, but information on the gene-transduced cells is not yet available. About 10 percent of the administered dose has been found in tumor sites of the first 5 patients tested using that approach.

- Although indium-111-labeled TILS can image tumor deposits as well as or better than almost any monoclonal antibody that has been used, increasing the amount of indium to enhance therapy is not feasible because TILs are cleared by the spleen and liver.

## VI. REMARKS BY THE ACTING DIRECTOR OF NIH--DR. WILLIAM RAUB

Dr. Raub said his purpose in addressing the Board was to share with them the challenge of maintaining a high-quality environment for research and for research administration, with special emphasis on intramural research. Although salaries are an important aspect of the problem, Dr. Raub stated that his remarks would focus on buildings, facilities, and support services.

Within the NIH appropriation structure, each Institute is a discrete entity with its own appropriation, and funds cannot be moved among appropriations without changing the law. The Buildings and Facilities appropriation provides the vehicle for funds for construction projects, both new buildings and major renovations, and support system development. Dr. Raub said that while NIH, like other institutions, has often been guilty of deferred maintenance, it is clear that modern science cannot progress without modern, well-run and well-supported facilities. In presenting historical information on Buildings and Facilities, Dr. Raub remarked that no pattern is discernible from year to year on how much money is appropriated, but it is always well under 1 percent of the total NIH budget. For the past 2 years, the President's budget has included $5 million for repairs and improvements, which Dr. Raub said is the base sum that permits continued operation of the campus.

Dr. Raub provided several reasons why NIH's revitalization is essential: demand for research and patient care is increasing, which means more space and more sophisticated and higher capacity utilities and other supporting services; new technologies require new, stringent safety measures for laboratories and patient care; the buildings and support systems are old, making it increasingly difficult to keep up with repairs; and major items of equipment and

components of the support system are obsolete and cannot be repaired or easily replaced. He stated that in the long run, the capacity of the infrastructure is simply not great enough to meet the requirements of the expanded campus. He cited, in particular, the problems of the Clinical Center, including the need to retrofit patient care and laboratory units to bring them up to current safety standards, modernization of patient care units and laboratories, and infrastructure problems.

Rehabilitation of the oldest laboratory buildings is being accomplished by what Dr. Raub termed "round robin renovation," meaning that the buildings are sequentially emptied for renovation with staff moved to other buildings. This sequence of renovation is expected to be completed by the late 1990s.

Dr. Raub added that the operation of animal facilities is another important aspect of the buildings and facilities problem. To ensure that NIH continues to exert a leadership role in this area, Dr. Wyngaarden had made commitments to take all appropriate steps to ensure the accreditation of all NIH animal facilities. In some instances, this has required the complete refurbishment of facilities. This process is expected to be completed in about a year.

Dr. Raub listed several construction projects in progress or being planned, including a child health and neuroscience laboratory facility now being added to building 6, addition of three floors to the A wing of the Clinical Center for expanded AIDS research, planning of a new medical intensive care unit for the Clinical Center, planning of a consolidated office building for those who administer the extramural programs, and planning for an FDA research building.

Excluding these major construction projects, Dr. Raub estimated that the continued revitalization of NIH over the next decade would require approximately $1 billion. This will require that all Institutes recognize this need and set priorities and make tradeoffs to ensure that the revitalization occurs. In addition, Dr. Raub said that it will be necessary to be sensitive to the kindred needs of extramural research institutions. While he acknowledged that no simple solutions were feasible, Dr. Raub urged that systematic planning be undertaken to deal with these long-term issues.

In discussion, the associated personnel problem was raised. Dr. Raub acknowledged that NIH is increasingly in the situation of not being able to retain first-rate senior scientists, with both salaries and facilities being important factors in the problem.

Dr. Howard Temin suggested that the Board support an increase in the Federal excise tax on cigarettes with funds earmarked for supporting the bypass budget and for NIH and other health-related facilities. Dr. Korn noted that California had passed a proposition to put a $0.25 tax per package on cigarettes with all money raised going into the health care system. It was suggested that the recommendation for excise taxes be broadened to include state legislatures.

Dr. Bragg moved that the Board support such a recommendation for an excise tax. Dr. Mihich seconded the motion, and the motion was unanimously approved.

## VII. CANCER CENTERS: CURRENT STATUS AND FUTURE PERSPECTIVES-- DR. SIDNEY SALMON

Dr. Roper introduced Dr. Salmon, Director of the Arizona Cancer Center and President of the Association of American Cancer Institutes (AACI), to continue the ongoing dialogue on cancer centers from the perspective of the cancer center community.

Dr. Salmon stated that he would review cancer center status and future perspectives from the standpoint of his roles as director of a cancer center, NCI adviser, and President of the AACI. He began by emphasizing the importance of NCI's leadership in the evolution of the Cancer Centers Program, beginning with the development of the core grant mechanism in the 1970s. He noted that this mechanism, along with NCI planning grants, conveyed funding to support the scientific infrastructures in selected institutions with major cancer research programs to promote greater advances. These funds enabled cancer research to have a priority in the selected institutions that it would not have within the traditional administrative structures. The result is that most cancer centers are matrix organizations that cut across traditional academic lines and facilitate multidisciplinary communication and research.

On a map of the United States, Dr. Salmon pointed out that the current locations of comprehensive, clinical, and minority consortium centers correspond with U.S. population centers and centers of research excellence. However, even with the addition of minicenters directed toward prevention and therapy (NCI's Community Clinical Oncology Program network), many areas in many states are without cancer centers.

Dr. Salmon described the Arizona Cancer Center, University of Arizona, Tucson, as an example of an individual center that evolved under the NCI program, beginning with a planning grant prior to the center's establishment in 1976, and a center core support grant (CCSG) that was awarded in 1978. He said that additional funds from the state help to stabilize the center and provide for activities, such as outreach, that are not supported by CCSG funds according to the current guidelines. He remarked that the Arizona center received one of the last NCI construction grants that was awarded, and he underscored the importance of this grant mechanism in stimulating philanthropic activity and providing leverage to other resources because of national recognition that the availability of NCI construction funds brought.

Dr. Salmon then described several studies conducted at the Arizona Center to illustrate that research at NCI-designated cancer centers focuses on areas unique to the communities they serve. He noted that any other center could provide similar examples of its own research. After listing funding categories permitted by CCSG guidelines, he emphasized the particular importance of the core (shared) services and developmental support categories to the studies he would be describing. Ongoing studies that reflect the unique needs of the Arizona Cancer Center community include: (1) development of a population-based skin cancer registry to identify all cases, including basal cell and squamous cancers and melanoma; (2) melanoma research that spans basic science, intervention studies, and therapeutic trials (including biologicals); (3) intervention program for research in nutritional- and chemoprevention of skin cancer; and (4) a pilot study that demonstrated the efficacy of beta-carotene therapy for oral leukoplakia, which is a preliminary to a larger study to determine the need to maintain therapy to sustain regression of the premalignant lesion. The center also sponsors the state-funded "Arizona Sun Awareness Program," which focuses on education for cancer prevention.

To illustrate the Arizona Cancer Center's strength in pharmacology and clinical trials, Dr. Salmon described research on the P-glycoprotein and its relation to multidrug resistance. Data from recently completed trials, which were published in the *Journal of the National Cancer Institute*, demonstrated that P-glycoprotein expression in human tumors would predict treatment resistance to certain classes of drugs. In a subsequent effort, a treatment protocol was developed to attempt to reverse drug resistance, which included a combination of cyclophosphamide, vincristine, adriamycin, and dexamethasone (C-VAD) plus verapamil. Dr. Salmon summarized the clinically relevant accomplishments of these studies as the immunohistochemical identification

of multidrug resistance, quantification of the degree of resistance, and development of successful approaches to reversing multidrug resistance in patients with myeloma or lymphoma. Other modulating agents under study include quinine sulfate and quinine plus low-dose verapamil.

Dr. Salmon noted that confirmatory studies have been approved and are operational in the Southwest Oncology Group to treat patients with non-Hodgkin's lymphoma and multiple myeloma. He observed that the transition from an observation in a single center to independent testing in the cooperative group setting is an important transition and further illustrates the uniqueness of the Cancer Centers Program. He pointed out that these studies underscore the importance of the core grant mechanism in providing funds for clinical research investigations at a point when there are only pilot observations made in the laboratory.

Dr. Salmon reviewed the legislative history of the program beginning with congressional interest in the eight state and privately organized centers that received partial funding from NCI in the late 1960s. The Yarborough Report in 1971 set the framework for the National Cancer Act and recommended the creation of a national network of comprehensive cancer centers to attain a critical mass of talent needed to combat cancer. The National Cancer Act laid the statutory groundwork for the program and mandated geographic distribution, community programs, and outreach. Subsequent reauthorizations expanded the numbers of centers, added basic research and public information centers, urged better geographic distribution and outreach programs, and extended core grants from 3 to 5 years. The focus in the late 1980s has been on improving the level of funding for the centers.

Dr. Salmon observed that this focus together with increasing concern over the lack of Administration support and authorization of the Institute of Medicine (IOM) report are indications that Congress considers the centers to be a regional and national resource. He then identified problems faced by NCI-designated centers in the 1980s due to reduced emphasis on the program by NCI and NIH, including reorganization and relocation of the program to the DCPC (with a loss of name identity), steady erosion of cancer center funding as a percentage of the total NCI budget, and decline in the number of centers and dollars in the latest budget. He reviewed the status of the program as of September 1989 as follows: 60 CCSGs are in force, of which 5 are due to phase out in FY88 and FY89; there are 58 NCI-designated cancer centers (19 comprehensive, 21 clinical research, 2 consortium, 1 comprehensive/consortium, and 15 basic science); 18 centers have pending applications for FY90 (1 new, 17 recompetitions).

Dr. Salmon summarized the recommendations to NCI contained in the IOM report as follows: (1) strengthen core support for cancer centers to exploit advances in prevention and treatment of cancer, (2) take steps to avoid a funding crisis in 1989 and develop an adequate budget for 1990, (3) develop a systematic program plan to ensure fiscal, managerial, and organizational resources with scientific oversight, and (4) increase representation of cancer centers in NCI planning and decision-making processes, including representation from an external advisory committee. He then commended Drs. Broder and Roper and NCI staff for actions taken to address those issues, including the June 1988 meeting with center directors, development of criteria for comprehensiveness (led by the NCAB Subcommittee on Cancer Centers), establishment of the Cancer Centers Program Planning Committee with extramural consultants nominated by center directors, and the meeting to discuss development of a 5-year plan for the Cancer Centers Program. He applauded the recent Senate Appropriations Committee action in restoring funds in its budget markup to maintain the present size of the program.

Finally, Dr. Salmon presented a summary of the role played by the AACI, which serves as a forum for cancer center leadership, both NCI-designated and other major centers. He pointed

out that AACI has regularly and routinely supported the NCI budget in Congressional deliberations. A recent project of the AACI has been the initiation of an electronic networking program to facilitate communication among the centers on issues such as clinical research, construction, patient identification for given protocols, and legislation.

In closing, Dr. Salmon expressed the opinion that prospects for the Cancer Centers Program were improving, and he attributed the change to actions taken by NCI leadership in addressing the problems that were raised in the IOM report.

In discussion, the following views were expressed:

- While core grants support infrastructure resources conducive to successful investigator-initiated research, as well as provide resources that make large P01s possible, a shift of funds from research grants to CCSGs would not be desirable.

- It is essential that centers achieve good priority scores, and within that context, that a critical mass of centers be maintained.

- Being located at very well-established centers and the effectiveness of the core grant mechanism confer an advantage on applicants from those institutions in the competition for R01s and P01s. Areas of the country that do not have an NCI-funded cancer center may be at a disadvantage in competing for R01 and P01 grants. They might not look favorably on a Congressional mandate to benefit the centers.

- The problem of maintaining a balance in the kinds of cancer centers funded (basic science, clinical, comprehensive) or attempting to tie an increase in the total centers budget to the sum of other NIH grant funding cannot be solved directly through the peer-review process; some type of administrative solution may be needed.

## VIII. CANCER CENTERS PROGRAM: 5-YEAR PLAN--DR. MARYANN ROPER

Dr. Roper began by quoting from the IOM report the recommendation concerning the development of a "systematic program plan during the coming year to ensure adequate fiscal, managerial, and organizational resources, coordination with related programs, and effective scientific oversight for the Cancer Centers Program." She stated that in response to that recommendation, NCI has begun a process for the writing of a 5-year plan, and she invited Board members to participate in the process as they saw fit. She identified the members of the NCI committee and their affiliations as follows: Ms. Judith Whalen, Planning Officer; Dr. Peter Greenwald, DCPC; Dr. Werner Kirsten, Frederick Cancer Research Facility (FCRF); Dr. Michael Grever, DCT; Dr. David Longfellow, DCE; Dr. Faye Austin, DCBD; and Mr. William Wells, Grants Administration Branch, OD, NCI. She noted the recent addition of Drs. Alan Rabson and Brian Kimes, DCBD, to the committee to reflect the move of the program. She said the committee has met approximately every 2 weeks since the end of July, including a meeting (August 8) with the ad hoc group of consultants elected by the cancer center directors to be their representatives in program activities. This consultant group includes Dr. Shirley Lansky, representing consortium centers, Drs. Alan Owens (Johns Hopkins University) and Alan Sartorelli (Yale University), representing comprehensive cancer centers, Drs. Walter Eckhard (Salk Institute) and Philip Sharp (MIT), representing basic centers, Dr. John Ultmann (University of Chicago), representing clinical centers, and Dr. Salmon, representing the AACI.

Dr. Roper noted that the issues addressed in generating the 5-year plan would include both scientific or programmatic and administrative issues, such as how funds are to be spent during the period of the plan and how the Cancer Centers Program should be aligned with other major NCI programs in terms of the recent comprehensiveness guidelines and goals for the year 2000. She added that the committee plans to address the Congressional mandate for centers both in terms of what they are currently doing and what directions should be followed to maintain a balanced program. Other discussion focused on creative financing measures that might be taken to address new program initiatives in light of the consensus that when new programs are undertaken, there should be funds to support them. Likewise, the committee addressed the issue of what can be done with the money currently available.

Finally, Dr. Roper stated that the committee intends to circulate the draft plan to the ad hoc consultants and the NCAB Subcommittee on Cancer Centers for approval before it is activated. She asked that questions or comments from Board members be submitted before the end of February 1990 to permit completion of the draft for hearings scheduled for the spring.

## IX. CLOSED SESSION

A portion of the first day of meeting was closed to the public because it was devoted to the Board's review of grant applications. A total of 1,240 applications were reviewed, requesting support in the amount of $215,342,838. Of these, 1,154 were recommended for funding at a total cost of $173,586,539.

## X. FAMILIAL POLYPOSIS--DR. PETER GREENWALD

Dr. Greenwald presented the results of a study by Dr. Jerry DeCosse and his colleagues of rectal polyps in 72 familial polyposis patients who had ileorectal anastomosis. The average age of the patients was 35 years at the beginning of the trial, and each patient had an average of 11 polyps at baseline. Some 10 patients dropped out before the beginning of the trial, and therefore 62 patients were randomized into three groups: a control group which received a placebo of vitamins and a low-fiber bran placebo; a vitamin group which received vitamins C and E and a low-fiber bran placebo; and a high-fiber, high-vitamin group which received vitamins C and E and two small serving boxes of All-Bran per day.

Dr. Greenwald explained that the patients underwent proctosigmoidoscopy every 3 months for the 4-year duration of the study. The basic study endpoint was the ratio of polyps at examination at the end of the study to polyps at baseline, with a declining ratio indicating efficacy. The study was, however, limited by its small size and the fact that there were a fair number of dropouts. There was also considerable variability in compliance between patients and between visits.

Dr. Greenwald reported that the results showed that in 15 of the 16 visits during the study the polyp ratio improved for those on dietary fiber. The vitamin group was slightly, but not significantly, below controls. When the results of the study were adjusted for compliance, there was a significant and consistent finding that the high-fiber group had fewer polyps.

In discussion, Dr. Greenwald emphasized that although the study was small, it represents the first time data from a randomized, intervention trial support the fiber hypothesis derived from epidemiologic and carcinogenesis data.

## XI. AMERICAN STOP SMOKING INTERVENTION STUDY FOR CANCER PREVENTION (ASSIST)--DR. PETER GREENWALD

Dr. Greenwald began his presentation on the ASSIST program, noting Dr. Erwin Bettinghaus' and Mrs. Helene Brown's involvement, by reviewing the history of the smoking program. He illustrated the average per capita cigarette smoking patterns over the previous century, noting the impact on these patterns of the first Surgeon General's Report, the FCC fairness doctrine, and the "nonsmokers' rights" movement. He stressed that the aim of NCI's Smoking, Tobacco, and Cancer Program (STCP) is to effect a steep decline in smoking in the second half of the century equivalent to the sharp increase in the first half of the century.

Dr. Greenwald explained that the focus of the STCP has, since the early 1980s, been on research on intervention. Current initiatives include intervention programs for children, youth, and other special populations, such as women, blacks, and Hispanics. One intervention study called COMMIT, which focuses on heavy smokers, involves 11 communities plus controls and aims to reach 2.5 million smokers.

Dr. Greenwald stated that the ASSIST program represents a collaborative effort between the NCI and the American Cancer Society (ACS) to develop comprehensive tobacco prevention and control coalitions to reach 50 million people in 20 states and metropolitan areas. The proposed budget for the ASSIST intervention is about $150 million over about 10 years, awarded as competitive contracts to health departments. The Request for Proposals (RFP) will be issued in December 1989 or early in 1990, with Phase I of the program beginning in 1991.

Dr. Greenwald stated that the specific objective of the program is to accelerate the reduction of tobacco use by applying proven tobacco control interventions. He explained that the size and complexity of the tobacco problem make coalitions the best vehicle for planning and delivering comprehensive interventions. Illustrating the general scheme of the program, Dr. Greenwald outlined the plan for the ACS Divisions and state and local health departments to form coalitions to plan and deliver smoking prevention and control interventions, with the main thrust through the media, policy, and specific program services in such settings as health care institutions, self-help, schools, and work sites. In Phase I of the project, coalitions will be formed and intervention plans will be established. In Phase II the plan will be implemented and evaluated.

In summary, Dr. Greenwald illustrated the timeline from 1988 through 1998 which showed that as the current smoking, tobacco, and cancer trials are completed, the funds for these will be shifted into the ASSIST program so that there will be little incremental cost in broadening the population impact.

In discussion, Dr. Greenwald clarified that the STCP is the broad overall name of the entire NCI program in the smoking area. The COMMIT program, which focuses on heavy smokers in the community, and the ASSIST trial, which targets a much broader group of some 50 million of the U.S. population, are components of the NCI STCP. Physician education about how to apply the results of previous stop-smoking intervention trials in helping their patients to quit smoking will be part of the ASSIST program.

## XII. SURAMIN THERAPY: STATUS OF EXPERIMENTS--DR. CHARLES MYERS

To introduce Dr. Myers' presentation on the suramin trial, Dr. Roper noted that this trial is one of the few positive Phase II trials. She informed the Board that suramin was used initially in AIDS therapy and commented that the attempted use of suramin against AIDS resulted in the AIDS program contributing to cancer research.

Dr. Myers stated that although the paradigm for cancer drug development since the 1940s had been to seek differential cytotoxicity using agents with broad toxicity patterns, about 10 years ago the increased understanding of the biology of malignant transformation had shifted the focus of drug development to specific agents that interfere with aspects of the biochemical processes whereby the *onc* genes cause this transformation. He pointed out that suramin stands out as the first of those agents. As background to his presentation on the suramin trial, he explained that many of the *onc* genes that lead to malignant transformation interfere with the process by which growth factors regulate cell growth. An important part of the normal control of tissue growth is through modulation of the production of peptide growth factors produced by surrounding tissues or other sources which then bind to cell-surface receptors and trigger signal transduction which controls the rate of cell growth. Malignant transformation can occur in this normal regulatory system by an overproduction and release of a growth factor that can then feed back and stimulate the growth of the cell that is producing it (an autocrine mechanism) and by changes in the cell-surface receptor and its signal transduction system, which can lead to unbridled cell proliferation.

Dr. Myers stated that the activity of suramin is probably due to antigrowth factor activity and that the effect of suramin can be overcome by addition of excess exogenous growth factor. Suramin can bind to and inhibit PDGF by preventing this growth factor from associating with its cell-surface receptor. Suramin displaces PDGF from its receptor by binding to the growth factor. Suramin also has antagonistic activity to TGF-beta, FGF, and EGF.

Dr. Myers stated that initial trials with suramin focused on prostate cancer for a variety of reasons, particularly because it is the most common cancer in men and because the only existing treatment for metastatic prostate cancer is hormonal therapy, which is not curative. He showed the results of a large, randomized, controlled trial comparing leuprolide with leuprolide and flutamide combination therapy, noting that leuprolide inhibits testosterone production and flutamide blocks the action of androgens at the tumor cell site, thereby overcoming adrenal androgen production. The results of this trial, representing the best response attainable with hormonal therapy, were a complete response rate of 7 to 8 percent in both arms of the study, a partial response rate of 28 and 36 percent for leuprolide and the combination therapy, respectively, and a total response rate of 35 and 43 percent, respectively, with a duration of response of only 14 and 17 months, respectively. In response to a question from Dr. Korn, Dr. Myers stated that the patients in this study had prostate cancer of ECOG performance grade 2 or better and that the earlier the disease was treated the better and more durable the response.

Next, Dr. Myers explained further why prostate cancer was selected as the initial focus of suramin trials. First, FGF-like activity is present in the normal prostate gland in high concentrations, and FGF concentration increases in prostate cancer. Suramin has been shown to inhibit growth of prostate cancer cell lines *in vitro*, and this inhibition can be overcome by addition of exogenous FGF.

Dr. Myers stressed that designing and executing clinical trials of prostate cancer is difficult because these patients tend to be older and do not generally tolerate cytotoxic therapy well. In addition, 85 percent have bone involvement only, while only 15 percent have measurable soft tissue disease. Therefore, because bone healing is slow in this age group, evidence of response to therapy requires 6 to 12 months to appear. In the absence of patients with evaluable disease, markers of prostate cancer have been sought, and prostate-specific antigen (PSA) has been established as a good measure of the bulk of tumor mass. Thus, the only reliable indices of response in prostate cancer are measurable decline of soft tissue disease; healing of bone lesions, which is difficult; and a decline in PSA.

Dr. Myers explained that based on these indices, patients for the suramin trial were deliberately selected for bidimensionally measurable disease. Of the 35 patients in the trial, 14 had bidimensionally measurable disease and 21 had bone involvement only. The patients in the study were younger than prostate cancer patients in general and had less well differentiated and more aggressive tumors. Dr. Myers reported that of the 14 patients with measurable soft tissue disease, 3 (21 percent) have had complete resolution of all soft tissue disease, typically within the first cycle of therapy. All of these patients also had bone involvement but have not been followed long enough to determine whether the bone disease will resolve. In 4 additional patients there has been a greater than 50 percent decrease in the diameter of all measurable tumors for more than 1 month. Overall, therefore, 7 of 14 (50 percent) have had a least a 50 percent decrease in the diameters of measurable tumor for one month.

Dr. Myers commented that this response places suramin as the most active chemotherapeutic agent available for prostate cancer and indicated that it may be approximately equivalent to that of hormonal therapy for previously untreated patients. He added that the patients in the suramin trial had, in fact, all failed previous hormonal therapy before being put on the trial. He noted that this population would normally live only 6 to 10 months.

Dr. Myers also illustrated the time course of response in the patients who have shown responses. He explained that the drug is given by continuous infusion for approximately 2 weeks, patients are monitored for 2 months and then treated again. He pointed out that for most patients a complete resolution of disease, if it is going to occur, occurs within the first cycle of therapy. He reported that the PSA index, especially in the patients with bone involvement only, also showed most of the decline before the second cycle of therapy was initiated. Of the 32 patients with initially elevated PSAs, 16 have shown at least a 50 percent decrease in PSA level. He stated that the usual sine wave variation of PSA levels in normal individuals is approximately a 20 point rise and fall over time and that the PSA level changes in the patients in the suramin trial far exceed this usual variation.

Dr. Myers stated that two observations from this study suggest that suramin may be of value in prostate carcinoma: the magnitude and frequency of soft tissue response, which is better than that to any other chemotherapeutic agent and almost equivalent to that attainable with first-line hormonal therapy; and the frequency with which PSA levels decline. He informed the Board that multi-institutional confirmatory trials have begun at Memorial Sloan-Kettering, Mayo Clinic, and M.D. Anderson. He also pointed out that the suramin trial has been conducted very quickly; the first prostate cancer patient was treated with suramin in a pilot study in July 1988, the Phase II study was initiated in November 1988, and in August 1989 the confirmatory studies began.

Dr. Myers turned to a discussion of the design for future studies of suramin, expressing concern about giving suramin alone to patients with hormonally responsive prostate cancer because testosterone appears to reverse the effects of suramin. He indicated that the design of

the next study would probably be castration plus flutamide versus castration, flutamide, plus suramin. This study would effect removal of testosterone (i.e., complete androgen blockade) plus or minus suramin.

Dr. Myers also reported responses to suramin in other malignancies, noting that the biology underlying these responses remains unknown. He described responses in heavily pretreated lymphoma patients and one dramatic response in a patient with T-cell leukemia, suggesting that suramin may also represent a major new drug in the treatment of poor prognosis lymphoma patients.

In discussion Dr. Mihich pointed out that suramin decays very slowly and asked whether pharmacokinetics studies were being incorporated into the suramin trials. Dr. Myers explained that the fact that suramin exhibits extensive protein binding and has a slow, 45-day half-life dictates a long course and the 2-month delay between treatments. He emphasized the need for careful monitoring of blood levels of suramin and appropriate dosage adjustments accordingly to ensure safe use of the drug. Unlike most other anticancer drugs, the pharmacokinetics of suramin are far slower than the tumor response. Thus, in prostate cancer, an excellent correlation between blood level and response has been made--response begins as blood levels of suramin reach between 100 and 150 $\mu$g/ml in sensitive patients.

In response to a question from Dr. Korn about toxicity of the suramin, Dr. Myers stated that neurotoxicity evidenced as a demyelinating syndrome clinically similar to Guillain-Barré syndrome had appeared early in the suramin trial. This toxic effect does not occur, however, if the blood level of the drug is kept below 300 $\mu$g/ml. Suramin can also cause thrombocytopenia in heavily pretreated patients or those with bone marrow replacement, which limits the use of the drug in these cases. In addition, suramin caused anticoagulation in some patients early in the trial because it is a heparin analog, but this effect can also be avoided by monitoring and maintaining safe blood levels of the drug.

Dr. Broder emphasized that although suramin required considerable expertise for administration, it represents the only current option for hormonally unresponsive prostate cancer. He stated that the NCI is encouraging NCI-funded cancer centers to submit protocols for suramin treatment of prostate cancer and for basic research for which the NCI will provide drug supplies.

In response to a question from Dr. John Durant about the required level of expertise to administer and monitor suramin, Dr. Myers stated that the assay was straightforward and could be conducted by any trained pharmacologist. He also noted that the drug has been used for over 50 years to treat trypanosomiasis and is not expensive to manufacture.

Dr. Broder further stated that suramin has antiretroviral effects and was probably dropped as a potential anti-AIDS therapy on the basis of toxicities observed with one dosage schedule. He expressed the opinion that the drug should probably be reconsidered as an anti-AIDS agent on the basis of increased understanding of the drug's mechanism and methods of monitoring safe blood levels.

## XIII. OFFICE OF SCIENTIFIC INTEGRITY--DRS. ALAN RABSON AND BRIAN KIMES

To introduce Dr. Kimes, Dr. Rabson explained that Dr. Kimes had been selected by Dr. William Raub to organize the new NIH Office of Scientific Integrity (OSI), which will be one of two DHHS offices to monitor allegations of fraud and misconduct in the scientific community. The other such office, the Office of Scientific Integrity Review (OSIR), will be at the

Department level. Dr. Kimes' temporary assignment to establish the OSI will end November 1, 1989.

Dr. Kimes began his presentation by reflecting on his initial experiences in accepting his position with the OSI in April 1989 and providing a brief history of some of the rules and regulations leading to the creation of the OSI. He explained that although his initial reaction to the establishment of such an office was that it was unnecessary and contrary to his personal and professional priorities, he soon realized that the public perception of the credibility of scientists, and their institutions and Government managers was not high. In the first few months in his position, Dr. Kimes was involved in a series of Congressional hearings, including those of Representatives Dingell, Weiss, and Roe, in which the issues of protection of the "whistle blower," conflict of interest, the capability of Government to manage science, access to data and use of data generated by PHS support, and the ability of PHS-supported institutions to investigate allegations against their scientists were raised. Dr. Kimes noted that all of the investigative Congressional committees thus far have originated in the House rather than the Senate. He added that the Office of the Inspector General (OIG) had also recently expressed considerable interest in the OSI and in scientific misconduct. Based on the involvement of the Congress and the OIG in this area, Dr. Kimes stressed the need for a strong advocacy in the scientific community in order to maintain creative open environments where individuals can conduct scientific research without fear.

Referring to the publication in 1986 of the NIH "Policies and Procedures for Dealing with Possible Misconduct in Science" in the *NIH Guide*, Dr. Kimes stated that these policies and procedures were meant as an internal guideline for PHS staff use and, in the absence of formal regulations, consequently became an external guide to PHS-supported institutions. In this 1986 guideline, misconduct was defined as "(1) serious deviations, such as fabrication, falsification, or plagiarism, from accepted practices in carrying out research or in reporting the results of research; or (2) material failure to comply with Federal requirements affecting specific aspects of the conduct of research, for example, the protection of human subjects and the welfare of laboratory animals." Within this guideline various sanctions were also described, including:

- Group 1 sanction--e.g., a letter of reprimand
- Group 2 sanction--e.g., prohibition from participation in peer review groups for the PHS
- Group 3 sanction--e.g., debarment from receiving PHS support.

Dr. Kimes stated that in the handling of misconduct by the PHS from 1982 to 1989, each agency had its own system for following the *NIH Guide*. At the NIH, there was an Institutional Liaison Office and the NIH director could not become associated with any investigation but had to maintain a separate role so that he could evaluate whether an investigation had been fair, objective, and thorough.

Thus, a political debate arose about how misconduct should be handled in the PHS and whether the major role for monitoring and conducting investigations of PHS-supported institutions should be centered at the Department level or at an agency such as the NIH. This debate, Dr. Kimes explained, resulted in the decision to establish two offices: the OSI at the NIH, which will be the front-line office to monitor and conduct investigations; and the OSIR, which will review all decisions on investigations before forwarding them to the Assistant Secretary and possibly a debarment official. The major responsibilities of the OSI are to receive

allegations, including anonymous allegations; monitor investigations of PHS-supported institutions; conduct investigations of extramural misconduct, when necessary; conduct investigations of allegations of misconduct of intramural science; and promote responsible conduct of research in the prevention and education area. Dr. Kimes noted that the OSI has the responsibility for all misconduct allegations for the entire PHS.

Next, Dr. Kimes described the development of the final regulation defining how institutions should handle misconduct entitled "The Responsibilities of Awarding Applicant Institutions for Dealing With and Reporting Possible Misconduct of Science." The initial definition of misconduct read: "Fabrication, falsification, plagiarism, deception, or other practice that seriously deviates from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research; or (2) material failure to comply with Federal requirements that uniquely relate to the conduct of research." After review by the scientific community, several changes were made, including: the addition of "proposing research"; "deception" was eliminated; part (2) was eliminated completely; and a clause was added stating that honest error or differences of opinion or interpretations of data are not misconduct. In addition, Dr. Kimes emphasized that the responsibility for receiving and investigating allegations lies with the institutions that receive PHS support.

Dr. Kimes also explained the timeline and reporting requirements of investigations. Every institution has 60 days in which to conduct an inquiry into the validity of an allegation, during which the OSI and the PHS are not involved or necessarily informed. Once an investigation begins, it must be completed within 120 days. During an investigation, the OSI receives an inquiry report and at the end of an investigation, a final report. The PHS can also request, retrospectively, information about inquiries not taken to investigation stage by institutions.

Another serious aspect of the final regulation will be the requirement of an assurance from each institution, without which an institution cannot receive PHS support. Dr. Kimes reported that every institution must have assurances to the OSI by January 1, 1990, and that administration of this part of the regulation is currently a large responsibility for the OSI. Lastly, the final regulation also requires institutions to report generic data on areas of misconduct, number of allegations, inquiries, and investigations.

Dr. Kimes also described the philosophy and strategy of the OSI developed under his leadership. He stated that the OSI will maintain a close relationship with institutions and scientists, acting as a facilitator and collaborator in what should be regarded as a mutual responsibility. To ameliorate the problem that institutions may not have the expertise to conduct investigations, the OSI will provide assistance to institutions for conducting investigations and submitting appropriate reports. The OSI aims to eliminate conflict of interest and emphasize objectivity, thoroughness, and fairness in investigations. In so doing, the OSI will maintain flexibility in judgment and avoid instituting an inordinate number of rules and regulations.

Dr. Kimes emphasized the importance of the OSI becoming increasingly active in promoting responsible conduct of research. He stressed that the OSI should maintain the timeliness of the investigative process, absolute confidentiality at the institutional and Government levels, and protection of the accused as well as the accuser. He noted that following up on the publications of individuals in question to prevent the use of false data is also a difficult but important aspect of promoting responsible conduct of research.

In closing, Dr. Kimes named two documents that had been particularly helpful in establishing the OSI: the Institute of Medicine report on the responsible conduct of research in the health sciences; and *The Framework for Institutional Policies and Procedures to Deal with Fraud in Research* published by the Association of American Universities with other scientific societies. He noted that the OSI and the OSIR had endorsed the latter as the guideline for any institution involved in establishing such policies and procedures.

In discussion, the following points arose:

- The Roe committee proposed that legislation is needed to protect journal editors from litigation against them by authors of multiple-author papers when articles are retracted after some of the data therein have been proven false or fabricated by a formal investigation of scientific misconduct.

- The primary purview of the OSI will be misrepresentation of data and plagiarism in scientific research, not other serious deviations, such as financial fraud, which are the responsibility of other organizations within the PHS.

- The final report on an investigation should clearly delineate the chronology of the events of the investigation, including the allegation, the focus of the investigation, and the rationale for all conclusions. The OSI is providing institutions with examples of appropriate final reports.

- Difficulties may arise in finalizing an investigative report because of the individual's legal right to appeal an adverse decision.

- Extensions to the 120-day investigation period will be allowed, but the timeline has been set in an attempt to avoid prolonging investigations unnecessarily.

- All anonymous allegations must have a minimum of substance that allows rational, reasonable followup.

- Adequate resources have been allocated to allow the OSI to fulfill its mission.

## XIV. WOMEN'S LEADERSHIP SUMMIT ON MAMMOGRAPHY--DR. MARYANN ROPER AND MRS. NANCY BRINKER

Dr. Roper introduced Mrs. Brinker's presentation on the Women's Leadership Summit on Mammography to be held September 20, 1989, as part of the NCI and Susan Komen Foundation's program to increase awareness and use of mammography.

Mrs. Brinker first thanked Drs. Broder and Roper and the Office of Cancer Communications (OCC) for their efforts in helping to develop this program with the Komen Foundation. She presented statistics to be reported at the September 20 Summit, noting, for example, that whereas in 1960, 1 of 20 women developed breast cancer, in 1990, almost 1 in 9 women will develop the disease. She stressed the importance of mammography in detecting early stage breast cancer, stating that the 5-year survival rate is 90 percent when the disease is detected in its earliest stages. She noted that according to a 1987 survey, however, less than 40 percent of women aged 40 or over have ever had a mammogram. She stated that in 1989, 43,000 women

will die from breast cancer and that an estimated 30 percent fewer would die if all women followed mammography guidelines.

Mrs. Brinker emphasized that the NCI breast cancer screening education campaign will be a comprehensive, year-long effort. She described the new consensus on screening reached on June 27, 1989, by 11 medical organizations, including the NCI, which represents the first agreement of major groups on screening guidelines for women under 50 years of age. While there has been agreement that all women aged 50 and older should have mammograms, the new guidelines recommend that screening, including a clinical examination and a mammogram, begin by age 40 and be performed at 1- to 2-year intervals. Insurance coverage for screening mammograms is becoming more widespread, and 24 states now have laws mandating such coverage. The mammography objective of the year 2000 goals calls for annual mammograms for 80 percent of women aged 50 to 70 by the year 2000.

Mrs. Brinker informed the Board that the Women's Leadership Summit on Mammography, planned as a beginning to the Breast Cancer Screening Education Program and immediately preceding National Breast Cancer Awareness Month during October, will include approximately 220 women leaders from numerous private and professional organizations such as the American Association of Retired Persons, the National Education Association, the National Council of Negro Women, and the National Council on Aging. Mrs. Barbara Bush will be the keynote speaker, introduced by Dr. Louis Sullivan, and other speakers will include Drs. Broder, Roper, and Marc Lippman as well as Constance Horner, Under Secretary of the Department of Health and Human Services. Mrs. Brinker's co-chair for the for the Summit is Nina Hyde, fashion editor of the *Washington Post*. Participants in the Summit will be given a kit developed by NCI that includes materials such as payroll stuffers and newsletter articles to use in their own organizations' activities. Mrs. Brinker noted the problem of lack of physician referral of women for mammograms and stressed the goal of the program to make mammography an integral part of a woman's health care plan.

Mrs. Brinker added that the Komen Foundation had developed several PSAs featuring entertainers, which will be distributed through the NCI. The PSA featuring the jazz singer Nancy Wilson was shown.

Mrs. Brinker introduced Linda Cadigan, Executive Director of the Komen Foundation, and thanked her for her efforts in developing the Breast Cancer Screening Education Program. Mrs. Brinker also showed the Board the materials that will be included in the kit given to all Summit participants. In closing, she added that the expense of the September 20 Summit luncheon is being entirely underwritten by Bloomingdales, citing this as a model for private-public partnerships.

In response to a question from Dr. Temin, Dr. Roper and Mr. Paul Van Nevel described the evaluation process for the Breast Cancer Screening Education Program, which includes an initial questionnaire about participants' organizational profiles, periodic assessments of information and methods of delivery, as well as a process evaluation to track effectiveness of individual components of the program, and an ongoing national survey to trace changes in behavior and attitude.

Mr. Van Nevel also described another OCC campaign on smoking among minorities planned for fall 1989. He showed a PSA featuring Wes Unseld, coach of the Washington Bullets, which will be used in the Washington, D.C., area, and explained that this PSA will be used as a prototype for development of PSAs for every National Basketball Association city. He noted the

efforts of Mrs. Irene Pollin and her husband in developing the Unseld PSA. In discussion, the need for evaluation of the effectiveness of this antismoking program was emphasized.

Returning to the subject of mammography, Dr. John Antoine (Associate Director, Radiation Research Program, DCT) commented that the Centers for Disease Control (CDC) had recently begun a study of breast cancer from early detection to outcome of treatment in which the Radiation Research Program is involved because of their interest in mammography. Dr. Greenwald added that DCPC is collaborating with CDC and other Federal agencies in a program aimed at promotion of early detection of breast cancer involving state health agencies and the Association of State and Territorial Health Officers.

## XV. A FEW COMMENTS REGARDING MAMMOGRAPHY--DR. BERNARD FISHER

Dr. Fisher first addressed the potential efficacy of breast cancer screening, listing previous and ongoing studies in this area. He commented on the heterogeneity of these trials and noted that only four of the studies had been randomized, while the rest were case-control studies. The studies evaluated various combinations of one- and two-film mammography, physician examination, and self-examination, and varied in the number of and intervals between screenings as well as the follow-up period.

Dr. Fisher pointed out that the evidence for mammographic screening in women under age 49 rests with the HIP study, which was carried out in New York and has an 18-year followup, and in one of the Swedish studies, which also demonstrated a benefit in younger women. The BCDDP study demonstrated that 30 percent of small tumors that were detected were found in younger women, adding further justification for screening women under age 49. All of the studies demonstrated some benefit of mammography in postmenopausal women.

Dr. Fisher raised several questions about mammography that require further study such as how often to screen, how many mammographic views should be obtained, and the role of physical examination when done with mammography.

Dr. Fisher emphasized that mammographic screening also presents the opportunity to gain important information about the biology of breast cancer. He suggested that tumor biology studies should address the issues of differentiation characteristics and heterogeneity of large versus smaller tumors detected by mammography.

Dr. Fisher concluded his comments by congratulating Mrs. Brinker for her efforts and noting that screening efforts will also lead to a better outcome for patients whose tumors are detected early.

In response to Dr. Broder's request for comments about the radiation dose of mammography, Drs. Fisher and Bragg commented that the dose is very low. Although Dr. Fisher stated that radiation associated with mammography has not been linked with harmful effects such as increased incidence of breast cancer, Dr. Bragg urged that mammograms should be avoided in women under age 35 unless there are extraordinary indications because the only data that are available are largely extrapolated from high-dose studies of women over age 35.

Dr. Bragg stated that fewer than 15 percent of radiologists have received adequate training in mammography and reported that a specific examination in mammography for Board certification in radiology will be implemented in June 1990. He also commented on the high cost and low compliance in followup of mammographic abnormalities and emphasized the need for

development and evaluation of less costly verification techniques. In addition, he raised the point that mammography can detect 87 percent of breast cancers but that approximately 13 percent are blind to mammography so that a negative mammogram does not preclude or erase the risk of breast cancer.

## XVI. LENFANT COMMITTEE REPORT ON NIH RESEARCH TRAINING PROGRAMS--DRS. ALAN RABSON AND VINCENT CAIROLI

Dr. Rabson began by explaining that the Lenfant Committee was formed in April 1989 to investigate a particular concern of Dr. Wyngaarden's about the adequacy of NIH training programs for physicians. Dr. Wyngaarden asked Dr. Claude Lenfant (Director, National Heart, Lung, and Blood Institute), Dr. Carl Kupfer (Director, National Eye Institute), and Dr. Ruth Kirschstein (Director, National Institute of General Medical Sciences) to establish a committee to evaluate physician research training, training of clinical investigators in clinical trials and epidemiology, and to determine how the training grants were being used in non-M.D. training.

Dr. Cairoli reviewed briefly the reports of the three task forces of the Committee: the Physician/Scientist Training task force chaired by Dr. Lenfant; the Training Opportunities in Clinical Community-Based Study Designs and Methodology chaired by Dr. Kupfer; and the Predoctoral and Postdoctoral Training of Non-Physician Scientists chaired by Dr. Kirschstein. Dr. Cairoli summarized the major issues considered by the task forces as follows:

- Early recruitment of talented individuals into biomedical careers
- Integration of research training with clinical certification requirements
- New approaches and opportunities for research training, particularly in the areas of prevention and population-based studies and clinical trial design
- Training stipends
- Data collection.

In describing these issues, Dr. Cairoli listed the NIH mechanisms for research by physicians, including individual fellowships, participation on a training grant, career awards, physician/scientist awards, and clinical investigator awards. He noted that Dr. Greenwald had established a fellowship program in prevention in DCPC, and that Dr. Chabner and his working group with the FDA had developed a 3-year fellowship for training at the NCI in clinical oncology and drug development and at the FDA in drug regulatory science. He explained that an important problem is the comparatively low level of NIH stipends: the predoctoral stipend is $8,500 and the postdoctoral stipend ranges from $17,000 to $31,500 depending on experience, as compared to the average physician house staff salary of $29,000 to $30,000. In the area of data collection, Dr. Cairoli noted that an NIH subcommittee had been formed to determine uniform fields of data collection to allow collation of data among the bureaus, institutes, and divisions.

Dr. Cairoli explained that in considering the question of whether the T32 institutional training grant is worthwhile pursuing for training physicians in research, the Committee concurred that the T32 grant should be integrated with other training mechanisms to make it more efficient. The number of M.D. trainees obtaining R01 or R29 grants was found to be unacceptably low. In addition, more than 60 percent of physicians receive research training of only 12 months or less when 2 years is viewed as an absolute minimum.

Dr. Cairoli illustrated that as the length of training increases, the number of physicians who continue to perform research and successfully apply for NIH grants increases. He explained that in placing an emphasis on earlier recruitment of physicians to research, the Committee is considering using the institutional training grant to involve medical students in research during summers or other times off before they receive their doctorate degrees. He noted that the NCI has a cancer education grant that had been used in this manner.

In closing, Dr. Cairoli described the Committee's consideration of designing an overall 5-year training program that would include a minimum of 2 years on a training grant and then integration of research on an individual fellowship or a career award. After 5 years of training, trainees would be in a position to apply for an R29 FIRST award or perhaps even an R01 grant. The Committee will provide a final report by the end of 1989, after which an update on the recommendations will be presented to the Board.

In discussion, Dr. Cairoli clarified the concept of the 5-year training program and provided the example of a current program in surgical oncology which also allows trainees to utilize the institutional training grant mechanism in a flexible way according to three possible plans. The importance of training in both clinical trials and community case-control research was emphasized.

Dr. Cairoli also pointed out the need to strengthen the peer review of institutional training grants to ensure that all trainees receive an adequate amount of research training. He asked that program directors review progress reports on these grants carefully to identify problems early. In response to a question from Dr. Mihich, Dr. Cairoli stated that the number of institutional training grants in surgical oncology had doubled from 8 to 16 training programs in the 2 years since modification of this grant.

In conclusion, Dr. Cairoli emphasized the importance of flexibility in establishing a 5-year training program for physicians. Highlighting the problem of medical school graduates with significant debt accepting training stipends, Dr. Chabner suggested awarding fewer grants but paying higher stipends to promising candidates.

## XVII. BUSINESS ITEMS--DR. DAVID KORN

Dr. Korn called attention to the document "Request for Comment on Proposed Guidelines for Policies on Conflict of Interest" that had been distributed, and he asked that Board members review it and submit any comments they desired to make by December 15. He then asked Board members to review the wording of three drafts prepared in response to the previous day's discussions as follows: a letter to Senator Frank Lautenberg supporting his legislative initiatives relating to smoking on domestic flights; a resolution expressing the Board's support for a Federal excise tax on cigarettes that would be earmarked for health-related activities to be sent to Congress and the President; and a letter to appropriate Congressional committees expressing the view that construction grants should be awarded through the peer-review process, rather than legislative earmarking of funds for specific institutions. Changes were made as suggested.

Finally, Dr. Korn asked for and received a motion to approve the minutes of the previous meeting. The motion was seconded, and the minutes of the May 15-16, 1989, NCAB meeting were unanimously approved as presented.

## XVIII. LEGISLATIVE UPDATE--MS. IRIS SCHNEIDER

Ms. Schneider began the update with the announcement that Ms. Dorothy Tisevich would be returning to NCI on October 10 to assume the position of Legislative Liaison for the NCI. Ms. Tisevich is a former Deputy Administrative Officer for the DCT and currently the NIH analyst in the Budget Office of the Office of the Assistant Secretary for Management and Budget, DHHS. Ms. Schneider then thanked Ms. Sylvia Bennett and Ms. Lavonne Dragt for their assistance in the Legislative Office since the departure of the former Legislative Liaison, Dr. Mary Knipmeyer.

Ms. Schneider referred Board members to the complete listing of Congressional visits and hearings and legislation of interest that had been distributed. She proceeded to highlight some of them in her report.

With respect to Congressional hearings, Ms. Schneider reported that Assistant Secretary Mason, accompanied by Drs. Broder (NCI) and Anthony Fauci (NIAID) and Frank Young (Commissioner of the FDA), testified for the DHHS at a hearing held by Representative Waxman on the "parallel track" proposal for AIDS clinical drug development. A meeting was convened by Representatives Guy Molinari and Gary Ackerman with Drs. Broder and Roper and representatives of the FDA, Office of Technology Assessment (OTA), NIH Office for Protection from Research Risks, and advocates of Mr. Lawrence Burton's Immunoaugmentative Therapy (IAT). Discussion at the meeting focused on the OTA study now under way on how to evaluate nontraditional therapies, for which IAT is the case study. Ms. Schneider noted that the IAT advocates were seeking NCI support for a clinical trial of IAT, and it was emphasized that no U.S. clinical trial could be conducted without an FDA-approved IND. With an IND, however, advocates for a particular therapy could conduct a study through community physicians without Federal support. This was demonstrated by the recent approval of aerosolized pentamidine for AIDS patients.

Commenting on the issue, Dr. Broder emphasized that NCI has a primary mission to prevent and cure cancer and should not be viewed as a validating organization. He noted that any group that feels strongly about a particular therapy, such as that proposed by Dr. Burton, has the tools available to accomplish a proper scientific study. He added that NCI could consider any data that would be provided after an appropriate demonstration (as was done with aerosolized pentamidine), but this should not be viewed as a validating mechanism for ideas that do not come through the standard NCI peer-review process.

In response to a question about whether NCI assumes responsibility for making statements about questionable health care providers, Dr. Broder explained that NCI will make statements only on the basis of scientific information available to it. He stressed that NCI must adhere to the scientific method and operate according to the peer-review process. He pointed out that given the many good study ideas and present resource limitations, great care must be exercised in choosing studies to be undertaken.

Ms. Schneider continued the legislative update by highlighting the following items:

- Appropriations--$5 million contained in the Treasury, Postal Service, and General Government Appropriation to add six floors to the Eppley Institute in Nebraska.

- Animal Welfare--NIH has formed a legislative working group that meets bimonthly to review legislative issues regarding animals and submit recommendations for action to the DHHS; NIH also has a senior level working group.

  --PHS also has a working group on animal welfare, co-chaired by Dr. Raub and the Administrator of the Alcohol, Drug Abuse, and Mental Health Administration, which is preparing a report for Dr. Mason and will continue to meet to address upcoming animal issues.

  --Various amendments, as listed in the handout, to amend the Animal Welfare Act.

- Tobacco--bills to limit youth access to cigarettes.

Other legislation relative to the interests of NCI dealt with mammography screening, nutrition monitoring, dietary recommendations, effectiveness research for medical care, epidemiologic studies of the effects of radiation, occupational disease notification, minority health issues, rehabilitation research, and modification of NIH's salary structure.

## XIX. SUBCOMMITTEE REPORTS

### REPORT OF THE SUBCOMMITTEE ON CANCER CENTERS--DR. JOHN DURANT

Dr. Durant recalled that the additional criterion for comprehensiveness was based on the history of strong legislative interest in community service and outreach by cancer centers. Points raised in discussion of this criterion included the following:

- Community service and outreach are responsibilities of comprehensive cancer centers within the context of their funding.

- This criterion does not represent a new objective for comprehensive cancer centers, but rather codifies what these centers should be doing.

- Appropriate cancer prevention and control activities are research and demonstration type activities, rather than community service programs such as those operated by city, state, or county departments of health.

Dr. Durant moved that the eighth criterion be approved and that guidelines for implementing the criteria be drafted to reflect the Board's discussion. The motion was seconded and unanimously approved. The draft guidelines will be sent to Board members for review within one month.

The Board unanimously approved the subcommittee's report, which included listings of cancer centers in phase-out status and those to be reviewed in FY90.

### REPORT OF THE SUBCOMMITTEE ON PLANNING AND BUDGET--DR. LOUISE STRONG

Dr. Strong reported that subcommittee meeting had included a review of the 1990 budget, the President's budget, and the House and Senate budget markups. She called attention to budget projections if Gramm-Rudman-Hollings deficit reduction measures are implemented. The

overall decrease would be about $27 million for NCI, with most of the funds coming from the grants pool.

Dr. Strong also noted a list of suggested topics for the FY89-90 NCAB Biennial Report. She requested that Board members identify any scientific, administrative, or policy topics they would like included in the report. It is anticipated that a draft will be ready for the Board's review at the January 1990 meeting.

The Board unanimously approved the subcommittee's report.

REPORT OF THE SUBCOMMITTEE ON AGENDA WORKING GROUP--
DR. LOUISE STRONG

Dr. Strong summarized additional proposed measures to address the most effective way for Board Members to review summary statements and the overall status of research support. The overall system could probably be made more efficient for review if mailings of the summary statements were sorted by percentile or priority score and by preparation and mailing of a master list of rebuttal letters from principal investigators in their assigned programs.

Subcommitee members requested that additional summary information be provided and that special items for the January 1990 meeting include preparation of statistical information about funding mechanisms and changes over time, development of a listing of grants by investigator, and preparation of an update on the status of past NIH trainees with respect to their success in obtaining R01s, with particular emphasis on minority trainees. Mr. Philip Amoruso said he would investigate what statistical information is available and report to the Board at the January 1990 meeting.

There was continuing discussion about the scheduling of subcommittee meetings on Sunday evenings. Staff were encouraged to exercise other options, e.g., 7:00 a.m. Monday or Tuesday. The working group also indicated that it was too early to evaluate the various recommendations that have been implemented.

The Board unanimously approved the report of the working group.

REPORT OF THE SUBCOMMITTEE ON AIDS--DR. HOWARD TEMIN

Dr. Temin commended NCI's AIDS programs and new initiatives that had been presented at the subcommittee meeting. He noted in particular Dr. Obrams' discussion of the emerging problem of AIDS-related malignancies and the importance of developing a data base to follow AIDS patients on clinical trials and in epidemiology studies for the development of malignancies. In addition, Dr. Chabner had reported that NCI will continue to play the lead role in preclinical AIDS drug development. Dr. Temin pointed out the screening of antiretroviral agents had revealed that viruses that are important causes of cancer, such as hepatitis B virus, may be susceptible to anti-HIV agents.

Referring to the budget, Dr. Temin stated that NCI's AIDS budget is approximately 20 percent of NIH's total AIDS budget and that AIDS accounts for about 10 percent of NCI's total budget. Although division directors reported no problems regarding funding or FTEs for AIDS programs, the space problem remains an important concern.

The Board unanimously approved the subcommittee's report.

REPORT OF THE SUBCOMMITTEE ON ENVIRONMENTAL CARCINOGENESIS--DR. ROSWELL BOUTWELL

Dr. Boutwell reported that the subcommittee heard presentations from the NCI, FDA, and EPA on the plant growth regulator daminozide. NCI reported on the bioassay of daminozide, which concluded that under the conditions of the bioassay, daminozide was not carcinogenic in the male Fischer 344 rat or in the female B6C3F1 mouse. In the male B6C3F1 mouse the induction of hepatocellular carcinomas may have been associated with the test chemical. Daminozide was carcinogenic in the female Fischer 344 rats, inducing adenocarcinomas and leiomyosarcomas of the uterus. The FDA presentation stressed that of 700 samples of a number of commodities tested by the FDA, the highest levels of daminozide were 8 ppm, whereas the regulatory level in apples was 20 ppm. The presentation also pointed out the problems in risk communication. The EPA presentation discussed a technical overview of the EPA's risk assessment on daminozide and reaffirmed the original classification of daminozide as a probable human carcinogen and recommended that dietary levels be reduced to zero over 3 years.

Topics for future meetings might include (1) the broader issue of pesticides and (2) naturally occurring carcinogens, including compounds resulting from the cooking of meat.

The Board unanimously approved the subcommittee's report.

## XX. NEW BUSINESS

Dr. Walter Lawrence requested a presentation on clinical alerts as a future agenda item. Dr. Chabner will include such a discussion as part of DCT's program review at the December 1989 meeting.

## XXI. ADJOURNMENT--DR. DAVID KORN

There being no further business, Dr. Korn adjourned the 71st meeting of the National Cancer Advisory Board at 3:00 p.m., Tuesday, September 19, 1989.

12/1/89
Date

Dr. David Korn, Chairman