DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
May 6-7, 1991

Building 31, Conference Room 10
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[1]
May 6-7, 1991

The National Cancer Advisory Board (NCAB) convened for its 78th regular meeting at 8:00 a.m. May 6-7, 1991, in Building 31, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

Dr. Paul Calabresi (Chairman)
Dr. Frederick F. Becker (absent)
Dr. Erwin P. Bettinghaus
Dr. David G. Bragg
Mrs. Nancy G. Brinker
Dr. Kenneth Chan
Dr. John R. Durant
Dr. Bernard Fisher
Dr. Phillip Frost (absent)
Dr. Walter Lawrence, Jr.
Mrs. Marlene A. Malek
Ms. Deborah Mayer
Dr. Kenneth Olden
Mrs. Irene S. Pollin
Dr. Sydney Salmon
Dr. Howard M. Temin
Dr. Samuel A. Wells, Jr.

President's Cancer Panel

Dr. Harold P. Freeman
Dr. Geza J. Jako
Mrs. Nancy G. Brinker

Alternate Ex-Officio NCAB Members

Captain Bimal Ghosh, DOD
Mr. Robert F. Hennick, NIOSH
Dr. Theodore Lorei, DVA
Dr. Hugh McKinnon, EPA
Dr. Lakshimi C. Mishra, CPSC
Mr. James S. Robertson, DOE
Mr. Kevin Tonat, NIEHS
Dr. Ralph E. Yodaiken, DOL

Members, Executive Committee, National Cancer Institute, NIH

Dr. Samuel Broder, Director, National Cancer Institute
Dr. Daniel Ihde, 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 and Development Center
Dr. Alan S. Rabson, Director, Division of Cancer Biology, Diagnosis, and Centers
Executive Secretary, Mrs. Iris Schneider, Assistant Director for Program Operations and Planning

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[1] 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

Dr. Eve Ida Barak, Associate Program Director for Cell Biology, Division of Cellular Biosciences, National Science Foundation, Washington, D. C., representing the National Science Foundation.

Mr. Alan Davis, Vice President for Public Affairs, American Cancer Society, Washington, D. C., representing the American Cancer Society.

Dr. Robert W. Frelick, Past President, Delaware State Tumor Registry, Wilmington, Delaware, representing the Association of Community Cancer Centers.

Dr. Edward Gelmann, Professor of Medicine, Anatomy and Cell Biology, Vincent Lombardi Cancer Research Center, Division of Medical Oncology, Washington, D. C., representing the American Society of Clinical Oncology, Inc.

Ms. Catherine Hogan, Oncology Nursing Society, South Pasadena, California, representing the Oncology Nursing Society for Ms. Barbara E. Britt.

Dr. John Laszlo, American Cancer Society, representing the American Cancer Society.

Dr. W. M. Linehan, Society of Urological Oncology, representing the Society of Urological Oncology for Dr. Jerome Richie.

Dr. Edwin A. Mirand, Associate Institute Director and Dean, Roswell Park Graduate Division of SUNY-Buffalo, Buffalo, New York.

Mrs. Yvonne Soghomonian, Associate Director of the Candlelighters Childhood Cancer Foundation, Washington, D. C., representing the Candlelighters Childhood Cancer Foundation.

In addition to NCI staff members, meeting participants, and guests, a total of 21 registered members of the public attended the meeting.

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I. CALL TO ORDER AND OPENING REMARKS—DR. PAUL CALABRESI

Dr. Calabresi called the meeting to order and welcomed the newly appointed members of the National Cancer Advisory Board (NCAB) and the President's Cancer Panel. He noted that Dr. Samuel Broder would introduce these members later in the meeting during his report. Guests representing various professional associations and research foundations were introduced.

Dr. Calabresi announced that members of the public wishing to express views regarding items discussed during the meeting could do so by writing to the NCAB Executive Secretary, Mrs. Barbara Bynum, within 10 days after the meeting.

Dr. Calabresi then quoted from the Federal Advisory Committee Act to clarify, for the record, the statutory provisions guiding the structure and proceedings of NCAB meetings. He stated that the Board is meant to "be utilized solely for an advisory function"—with the exception of the review of grant applications, in which the Board's actions can determine the disposition of grant awards. Meetings must be open to the public except when the need for confidentiality concerning grant applications requires closed sessions. A designated employee of the Federal Government must convene, approve the agenda of, and attend each meeting; Dr. Calabresi noted that in the case of the NCAB that person is Mrs. Bynum.

Dr. Calabresi stated that the minutes of the February NCAB meeting had been distributed in the Board members' notebooks. He asked members to review them and said that he would call for their acceptance Tuesday, at the end of the meeting. He then announced the schedule for subcommittee meetings to be held Monday afternoon and evening. He stated that on Tuesday he would appoint a new subcommittee on Women's Health and Cancer, and invited members who were interested in serving on this committee to notify Mrs. Bynum.

II. FUTURE MEETING DATES—DR. PAUL CALABRESI

Dr. Calabresi called attention to the scheduled dates for NCAB meetings in 1992 and 1993, as listed on the agenda; he added that, while each meeting is scheduled for three days, the Board would continue to try to limit meetings to two days whenever possible.

Having received no objections to this schedule, he brought up a problem which he had already discussed with Dr. Broder concerning conflicts of the May meetings in 1992 and 1993 with the clinical investigations meeting usually held the first weekend in May. Dr. Samuel Wells suggested that the two May NCAB meetings be scheduled as two-day meetings beginning on Tuesday instead of Monday. After a discussion, the Board confirmed these new dates for the May NCAB meetings in 1992 and 1993.

III. REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE (NCI) —DR. SAMUEL BRODER

Introduction of New Board Members

Dr. Broder began his report by welcoming and introducing the new members of the President's Cancer Panel.

Mrs. Nancy Brinker, who will continue to serve on the NCAB until her replacement is appointed by the President, has served as the founding Chairman of the Board for the Komen Foundation in Dallas, Texas, since 1982. She is an outstanding advocate for breast cancer research and has been an extremely effective patient advocate.

Dr. Geza Jako is a physician, scientist, and professor and at the Boston University School of Medicine in Melrose, Massachusetts. He served previously on the NCAB from June 12, 1982, to March 8, 1988. He is an expert on laser surgery and the application of innovations in surgical science for the treatment of cancer.

Dr. Harold Freeman, who was appointed by the President to chair the Panel, is Director of Surgery for the Harlem Hospital and Professor of Clinical Surgery at Columbia University in New York City. He served as the National President of the American Cancer Society from 1988 to 1989. During that time he chaired hearings on poverty and cancer, and he has written extensively on that subject. The latest issue of the *Journal of the National Cancer Institute* contains an editorial by Dr. Freeman entitled "Race, Poverty, and Cancer."

Dr. Broder presented Presidential Appointment Certificates to each of the new members of the President's Cancer Panel. He then announced that the first meeting of the new Panel, on the topic of "Cancer and Poverty," will take place on July 9, 1991, at Wilson Hall on the National Institutes of Health (NIH) campus. Dr. Louis Sullivan will speak at the meeting.

Dr. Broder welcomed Ms. Deborah Mayer as a new member of the NCAB. She is a lecturer in Oncology at the Massachusetts General Hospital in the Institute of Health Professions in Boston and is past President of the Oncology Nursing Society. She established the first Biological Response Modifiers Clinical Oncology Research Unit at Frederick Memorial Hospital in Frederick, Maryland, and directed this unit from 1981 to 1983.

Dr. Broder then acknowledged the presence of two new ex-officio members: Dr. Theodore Lorei, representing the Department of Veterans Affairs, and Dr. Hugh McKinnon, representing the Environmental Protection Agency. He also announced several upcoming agenda items for the meeting: an update on the human gene therapy trials; a presentation on NCI's communication programs; a demonstration, during breaks, of the NCI's compact disk information systems; and an address by Dr. Bernadine Healy, the new Director of the National Institutes of Health, focusing on the establishment of the James A. Shannon Award and a comprehensive study on women's health.

New Developments Within the NCI

The NCI, Dr. Broder stated, will commit approximately $30 million to the Shannon Award system. The funding for the awards comes from two sources: the NIH Director's Discretionary Fund and the one percent NIH Director's Transfer Authority. The Shannon Award mechanism is designed to help scientists whose applications for regular research projects fall just below the pay line; the awards will help these scientists maintain their work and advance their ability to compete, but will not provide full funding. The NIH will provide $40,000 to $50,000 for a one-year period, or possibly up to $100,000 over a two-year period, for 300 to 400 of these applications; the NIH currently proposes to limit indirect costs for these awards to 20 percent.

The women's health study, Dr. Broder continued, will be cosponsored by the NCI, the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), and other categorical institutes; it will be coordinated by the Office of Research on Women's Health, NIH. He invited Board members to share any ideas or comments on the role of the NCI in this project.

Honors, Awards, and Staff Changes Within the NCI

Dr. Broder then announced that a number of NCI staff have recently received major honors: Dr. Steven Rosenberg, Chief of the Surgery Branch, Division of Cancer Treatment, received the Lifetime Science Award from the Institute of Advanced Studies in Immunology and Aging, and will also receive the Karnofsky Prize and give the Karnofsky Lecture at the American Society of Clinical Oncology meeting on May 20, 1991; Dr. Michael Sporn, Chief of the Laboratory of Chemoprevention, will receive the 10th Cain Memorial Award at the annual meeting of the American Association for Cancer Research (AACR) in mid-May for his pioneering work on TGF beta and the development of an assay system for testing a variety of retinoids and their analogs; Mr. Richard C. Carter of the Frederick Cancer Research and Development Center (FCRDC) has received the NIH Merit Award.

Dr. Broder announced the following NCI staff changes at the Division of Cancer Treatment (DCT): Dr. John Minna, Chief of the Navy Medical Oncology Branch, has retired, effective April 1, 1991, to assume the position of Director of the Cancer Center and Division Chief for Hematology/Oncology at the Southwestern Medical Center at the University of Texas at Dallas; Dr. Bruce Johnson has been appointed Acting Chief of the Navy Medical Oncology Branch; Dr. Joseph Tomaszewski has been appointed Chief of the Toxicology Branch, effective April 21, 1991. He announced the following appointments in the Division of Cancer Prevention and Control: Dr. George Alexander as Chief, Special Populations Studies Branch of the Cancer Control Program; Dr. Lawrence Bergner as Chief, Public Health Agency Section; Dr. Marc Manley as Chief, Applications in Prevention and Early Detection Section; and Dr. James Mulshine as Chief, Biomarkers and Prevention Research Branch in the Early Detection and Community Oncology Program. Two new branches have been established in the Early Detection and Community Oncology Program: the Biomarkers Prevention Research Branch and the Preventive Oncology Branch.

In the Division of Cancer Etiology (DCE), there have been two departures: Dr. John Lechner, Chief, In Vitro Carcinogenesis Section, Laboratory of Human Carcinogenesis, has joined the Inhalation and Toxicology Research Institute in Albuquerque; and Dr. Joseph Bolen, Chief, Biochemical Oncology Section, Laboratory of Tumor Virus Biology, has joined the Bristol-Myers/Squibb Company.

In the Division of Extramural Activities (DEA), Ms. Elise Kreiss has been appointed Chief, Administrative Management and Planning Branch; and Dr. Carolyn Strete, formerly Chief, Prevention, Epidemiology and Control Review Section, has been appointed Deputy Director for Extramural Activities in the National Institute of Mental Health.

In the Office of the Director, the Legislative Office, directed by Ms. Dorothy Tisevich, has been reorganized.

Discussion of Legislative Issues

Dr. Broder reported that the NCI participated in a number of Congressional hearings since the last NCAB meeting. At the Senate Appropriations hearing for the NIH chaired by Senator Tom Harkin (D-IA) on March 14, 1991, Senator Slade Gorton (R-WA) discussed the NCI appropriation level with then-Acting NIH Director Dr. William Raub. Dr. Raub noted that the minus six percent status of the appropriation since 1981 in constant dollars had occurred because during the 1980s the NIH placed an emphasis on research project grants while the NCI had large commitments in mechanisms such as Centers, Cooperative Groups, and Prevention and Control. He said that it is a goal of the NIH to address NCI needs and improve its budget situation.

Dr. Broder reviewed several topics discussed at the April 10th House Appropriations hearing for NCI chaired by Representative William Natcher (D-KY). He noted that, at this hearing, the NCI was asked to advise the Congress on whether there should be Federal legislation on standards for mammography and Pap testing.

Dr. Broder described a hearing before the Subcommittee on Aging of the Senate Committee on Labor and Human Resources chaired by Senator Brock Adams (D-WA). The hearing was entitled "The Role of Menopause and Gender Differences in Aging on the Development of Disease in Mid-Life and Older Women." He observed that the Subcommittee on Aging is the natural place for such an inquiry, as the median age for breast cancer and ovarian cancer is 63 years. Representative Patricia Schroeder (D-CO) testified for the Congressional Caucus for Women's Issues. Dr. Bernadine Healy, Director of NIH, testified, and was accompanied by Dr. Broder, Dr. Franklin Williams from the NIA, Dr. Claude Lenfant from the NHLBI, Dr. Lawrence Shulman from the NIAMS, and Dr. Florence Haseltine from the Center for Population Research, National Institute of Child Health and Human Development. Representatives of other Federal agencies, biomedical institutions, and the public also testified.

Dr. Broder noted that all components of the NCI, including basic research, clinical trials, education and information dissemination, and Cancer Centers, are committed to a comprehensive approach to women's health, with investigation efforts in prevention, early detection, tumor biology, treatment, and quality of life.

At the April 25th Senate Committee on Labor and Human Resources hearing on the 20th Anniversary of the National Cancer Act, chaired by Senator Edward Kennedy (D-MA), Mr. Tip O'Neill and other cancer survivors testified on behalf of cancer research. Dr. Emil Frei spoke on the National Cancer Program; Dr. Harold Freeman on poverty, minorities, and cancer; Dr. Maureen Henderson on prevention; and Drs. Broder and Lance Liotta on behalf of the NCI.

New Scientific Developments Within the NCI

Dr. Broder reported on some recent NCI activities. The research group headed by Dr. Bert Vogelstein at Johns Hopkins has further defined the multistep pathogenesis of colon cancer by identifying the potential first step in the development of that cancer. This group has identified a hierarchy of specific gene losses or mutations, including most recently the so-called MCC gene, in which MCC stands for "mutated in colon cancer."

He also described advances in hepatocellular cancer, involving the tumor suppressor gene on chromosome 17, known as P53, which likely plays a pivotal role in many cancers. Two groups of investigators, one headed by Dr. Curtis Harris of the Laboratory of Human Carcinogenesis in the Division of Cancer Etiology and another from the Massachusetts General Hospital, have independently found the same genetic changes in liver cancers from China and from Southern Africa. The culprit may be the mutagen known as aflatoxin, a toxic fungal by-product that contaminates food. This important research is expanding our knowledge of the molecular biology of environmental carcinogenesis.

A workshop on drug development, biodiversity, and economic growth was held on the NIH campus on March 13 and 14 with representatives from the United States Agency for International Development (AID), the Fogarty International Center, and the National Science Foundation. The objective was to encourage developing countries, particularly in tropical areas, to conserve the diversity of species, flora and fauna, to retain the potential of discovering new pharmaceutical agents. Representative John Porter (R-IL) expressed his interest in protecting the rain forest, biodiversity, and intellectual property rights of the developing world and asked Dr. Broder a number of questions at the appropriations hearings related to this topic.

During the meeting, the NCI Developmental Therapeutics Program (for discovery of anticancer and anti-AIDS agents and natural products) was discussed, including NCI contracts for collection of materials. A draft policy statement and material transfer agreement to govern the transfer of samples from NCI to outside investigators were presented. The meeting concluded with a presentation of a collaborative effort between AID and the National Science Foundation in which $2.5 million has been allocated for 12 biodiversity research programs in Latin America, the Pacific Islands, and Indonesia.

Finally, Dr. Broder reported on a new NCI service, Cancer Fax, designed to facilitate transmission of current information from NCI's databases to health professionals via the now widely disseminated telefacsimile technology. There is no cost to users other than the cost of their fax machines and telephone calls. The number for the Cancer Fax computer in Bethesda is 301-402-5874.

Discussion of the NCI Budget

Dr. Broder then moved on to a brief update on the NCI budget, primarily for the benefit of new members. The 1991 appropriation, after across-the-board cuts, is approximately $1.715 billion for the NCI ($1.55 billion for cancer and $160 million for AIDS) out of a total of approximately $8.3 billion for the NIH as a whole. The research project grant pool portion of the 1991 budget is approximately $789 million; the total for grants-in-aid is approximately $987 million, but not all grants-in-aid are considered research project grants. The Director of the NIH has statutory authority to exercise a 1 percent transfer from any NIH account to any other NIH account, and this year will exercise that authority in creating the resources necessary for the Shannon Award. This money will not come from the research project grant pool.

The 1992 President's Budget is $1.641 billion for cancer and just under $170 million for AIDS, for a total of $1.81 billion. If enacted into law, this would provide an increase of $87 million, or about 5.6 percent. The 1992 total for research project grants is approximately $846 million, for an increase of 7.2 percent. The increase for Cancer Centers in 1992 is 2.4 percent; for the Clinical Cooperative Groups, 6 percent; for the Intramural Program, 6 percent; for Research Management and Support, 14 percent; and for Cancer Prevention and Control, 4.8 percent. The Research Career Program and the Cancer Education Program budget are essentially flat, with no increase.

Dr. Broder said that the NCI was going to try to meet its allocated target goal of 840 new and competing grants this year; the total number of grants is expected to be almost 3,100. The percentage funded rate is expected to be about 27 percent by the end of the year. He explained that, in reaching the target goal, an R01 and a P01 each count as one research project grant. However, R01s are funded at an average of $170,000, while P01s average about four or five times that amount. Dr. Broder noted that when he took over as NCI Director, about 25 percent of the research project grant pool, by dollars, was committed to P01s, which accounted for only 5 percent of the total number of grants. With a little more than $200 million available for 840 new and competing grants, the P01 line is going to be very austere. He explained that the P01 line would not disappear, but it will be a significant challenge to fund all of the meritorious P01s in the Institute's portfolio.

In response to a question concerning the scope of activities encompassed by Research Management Support, which received the greatest increase, it was explained that $7 million of the $11 million increase in that line is attributed to a health interview survey planned for this year by the Public Health Service (PHS).

Dr. Broder responded to Dr. Wells' expression of concern about the lack of an increase in training grants by stating that he shared the Board's concern on this issue; he pointed out the need for a level playing field for all members of the National Cancer Program to have access to relevant training as well as opportunities to compete for funding instruments. Dr. Broder argued that while the National Research Service Awards (NRSAs) are extremely important, the NCI needs to look at other ideas. He suggested a presentation could be made at a future Board or subcommittee meeting on how the Institute plans to try to use the K Award system, particularly the K08s and K12s, to address some of the issues of training.

Dr. Broder continued with a brief discussion of plans for the P50 mechanism, a seldom-used core grant. The Institute wants to have P50s that allow interdisciplinary support for a specific disease; the diseases that will be emphasized are prostate cancer and breast cancer. In the area of prostate cancer, he said there is a need for a fresh look at prevention, diagnosis, and treatment research. With breast cancer, he added, a number of new basic science observations need further application. The P50 is an opportunity to identify people at an early stage in their careers and provide some flexibility for them. The NCI, he added, also wants to provide more flexibility for people to receive training under the auspices of the R01 mechanism.

Dr. Sidney Salmon expressed serious concern about any trend to reduce the P01 pool. He argued that P01s are the best mechanism for translating the advances of basic research from the laboratory into the clinic, with interaction between the two. Dr. Broder repeated his belief that the P01 mechanism is indispensable to the success of the NCI and emphasized a need for flexibility and for inter-institute diversity. He noted, for example, that the National Eye Institute makes little or no use of the P01 mechanism, whereas the NCI relies on it heavily. Dr. Erwin Bettinghaus suggested that the NCAB could make an official statement at this or a future meeting to help the NCI continue to maintain the P01 as an important funding instrument. (A motion to this effect was made and passed on the second day of the meeting.)

IV. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Dorothy Tisevich, the NCI's legislative liaison, made a brief report on the first few months of the 102nd Congress. In addition to the round of appropriations hearings described earlier by Dr. Broder, there have been hearings on reauthorization of NIH programs, women's health issues, and commemoration of the 20th anniversary of the National Cancer Act. Ms. Tisevich called attention to material in the members' notebooks describing a number of cancer-related bills that have been introduced.

There have been changes in committee memberships, she continued, that have resulted in a number of visits to the NIH campus by Congressional members and their staff. In April, Dr. Broder met with Representative Carl Pursell (R-MI), ranking minority member of the Labor, Health and Human Services, and Education Subcommittee of the House Appropriations Committee. Mr. Mark Weston, Minority Staff Director for the House Appropriations Committee, visited the NIH and was impressed with the NCI's PDQ system and outreach activities. Senator Harry Reid (D-NV), a member of the Labor, Health and Human Services, and Education Subcommittee of the Senate Appropriations Committee, spoke with Dr. Broder about the problems of recruiting young people into research careers and the financial burden facing medical school graduates. He expressed enthusiasm for the NCI's Summer Science Enrichment Program. Another visit involved staff of former Representative Guy Molinari and staff of his successor (and daughter) Representative Susan Molinari (R-NY). They met with Dr. Michael Hawkins of the Cancer Therapy Evaluation Program (CTEP) to discuss plans to facilitate and improve access to information needed to support the further conduct of clinical trials; NCI staff are developing a document to provide guidance for investigators who wish to generate interpretable data.

Ms. Tisevich reminded members that the NIH reauthorization passed by the 101st Congress last year established a National Foundation for Biomedical Research and a National Center for Medical Rehabilitation Research at the NIH but excluded a number of issues that had been included in the original legislation. During this current session those issues are again being considered. Representative Henry Waxman (D-CA) has introduced HR-1532, the NIH Revitalization Amendments of 1991; this bill includes provisions on fetal tissue transplantation research, women's health equity, the use of animals in research, scientific misconduct, whistle-blower protection, and many other issues. NCI-specific features of this bill include the elimination of the separate authorization of appropriations for research and prevention. The Department of Health and Human Services (DHHS) will submit a bill report in opposition to this legislation, recommending a simple extension of the authorities of the NIH.

To date, the Senate has not introduced an NIH reauthorization bill, but is expected to introduce a bill that will closely resemble last year's bill, which included the Women's Health Equity Act, a continuation of the moratorium on funding for human fetal tissue transplantation, and a continuation of separate authorizations for cancer research and prevention and control.

Ms. Tisevich highlighted a few other bills that have been introduced recently:

- Two bills introduced by Representative Mary Rose Okar (D-OH) to authorize additional funds for breast cancer research

- The Ovarian Cancer Research Act of 1991, introduced by Representative Patsy Mink (D-HI)

- Legislation introduced by Representative Frank Pallone (R-NY) to require the Department of Energy, working with the Environmental Protection Agency and the National Institute of Environmental Health Sciences, to study the potential human health effects of electrical and magnetic fields

- Legislation introduced by Representative Louis Stokes (D-OH) to establish, under the National Science Foundation, at least 20 summer science academies in math, science, engineering, and communications.

Ms. Tisevich called the members' attention to materials in their notebooks describing other recently introduced bills on such topics as AIDS, Medicare and Medicaid coverage for screening mammography, mammography quality assurance, and increased access to health care for underserved and disadvantaged women.

She added that the House is expected to hold hearings marking the 20th anniversary of the National Cancer Act, although no dates have been set. Dr. Broder is scheduled to present a luncheon seminar for Congressional staff on June 3rd, the second in a series of NIH seminars intended to educate Congressional staff on selected research programs and biomedical research issues. Later in June, Senator Brock Adams will hold hearings on breast cancer.

V. GENE THERAPY UPDATE—DR. STEVEN ROSENBERG

Background

Dr. Rosenberg spoke on the current status of gene therapy research for the treatment of cancer. He began by reviewing the development of immunotherapies for the treatment of cancer

over the last decade. The goal of these gene therapy studies has been to develop a method for mediating the rejection of human cancers using immune manipulations with recombinant cytokines and immune cells. The general approach that has been taken is called adoptive immunotherapy, defined as the transfer of immunologic reagents (immune cells in this case) with antitumor reactivity to the tumor-bearing host for these cells to mediate, directly or indirectly, antitumor effects. He explained that this approach involves identifying, in cancer-bearing patients, immune cells (lymphocytes) that are reacting against the cancer, isolating these cells, enhancing their antitumor activity, enlarging them in numbers, and returning them to the patient in an attempt to mediate antitumor effects.

Dr. Rosenberg reviewed some clinical trials performed in the past. All patients in these clinical trials have advanced cancer that has failed all standard treatment and have had no other treatment for the 30 days prior to or throughout the trial. They all have measurable disease and expected survivals of greater than three months.

Lymphokine Activated Killer (LAK) Cells

The first treatments utilizing adoptive immunotherapy involved a killer cell called the lymphokine-activated killer (LAK) cell, described in 1980. Dr. Rosenberg explained the process—taking peripheral blood cells from the cancer patient, isolating them on leukophoresis machines, and incubating them in culture with interleukin-2 (IL-2) to create LAK cells that can destroy cancer cells in culture. The LAK cells are reinjected back into the patient along with IL-2, which keeps them alive and expanding in the body.

Dr. Rosenberg reported that most of the first 178 patients treated with LAK/IL-2 have advanced renal cell cancer and melanoma. About 10% will undergo complete regression of all their metastatic disease. Another 10% of melanoma patients and 25% of renal cell cancer patients will undergo at least a partial regression (50% reduction) in their established cancer. Some responses are also seen in patients with colorectal cancer and non-Hodgkin's lymphoma.

Because of responses to high-dose IL-2 alone, a prospective randomized trial was completed involving 181 patients receiving either LAK/IL-2 or IL-2 alone. Dr. Rosenberg noted a higher incidence of complete responses in those receiving LAK/IL-2, although a good incidence of partial responses was evident in both groups. After three years, there has been an improvement in survival of patients receiving LAK/IL-2 , and follow-up is continuing. He reported that of the 19 patients that went into complete remission, eight remain so at 27 to 63 months. Furthermore, an advanced melanoma patient with approximately one-third of a lung replaced by melanoma went into a substantial partial regression, and a patient with hundreds of melanoma lesions underwent complete regression four years ago and remains disease free.

Tumor Infiltrating Lymphocyte (TIL)

The work with LAK/IL-2 led to research for cells with more potent antitumor effects. Dr. Rosenberg continued by discussing the finding of the tumor-infiltrating lymphocyte (TIL), a lymphoid cell that infiltrates into solid tumors and can be grown by culturing single-cell suspensions from these tumors and IL-2. These TILs, which have now been used in therapy, have served as the base for the introduction of foreign genes into humans.

Dr. Rosenberg emphasized that TILs are unique in that they are the only cell type yet identified that shows a specific reactivity against tumor antigens present on at least some human tumors. TIL cells can be isolated from approximately one-third of melanoma patients, and those cells will have unique reactivity against that patient's melanoma, but not the melanoma of another patient. These TIL cells indicate that at least some patients with growing malignancies do have

an existing immune reaction against their cancer. In the *Journal of Immunology,* Dr. Schwertzentruber describes a study that demonstrates that at least some breast cancer patients also have unique tumor-associated antigens. TIL cells have also been found in some patients with renal and bladder cancer.

In a related discussion, Dr. Rosenberg explained that certain melanoma antigens are shared among individuals who are carefully HLA typed and match at a single histocompatibility locus. This means that a patient whose TIL cells are capable of lysing his own melanoma can also lyse all melanomas that share the histocompatibility antigen, but cannot recognize tumors that do not share this histocompatibility. He commented on the important implications this holds for these antigens to be used for vaccination or immunization of patients against melanoma in an attempt to develop new treatments based on recombinant DNA technology. This has led to the first attempts to clone the gene that codes for the tumor antigens that are being recognized by these cells.

Tumor Antigen Cloning

Dr. Rosenberg described the process followed in his research in attempts to clone these genes. They begin by raising TIL cells that recognize tumor antigens on a patient's autologous tumor and then immunoselecting for autologous tumors that lack that antigen. A cDNA library is raised from the antigen-bearing tumor and transfected into the tumor lacking the antigen. The TIL cells are then used to recognize the transfectants as a way to identify the tumor antigen gene.

Dr. Rosenberg continued by discussing the first results, yet unpublished, of this process. A cDNA library was prepared from a patient with melanoma. The library has been screened to attempt to identify clones that can transmit the ability to recognize this antigen to lines that do not have it. One plasmid has been isolated, identified, and retransfected into the antigen-negative cells.

Dr. Rosenberg said this gene shares about a 97 percent homology with the DNA from a mitochondrial protein. In fact, recent results show that some minor histocompatibility antigens are actually mutated mitochondrial genes. He stated that if this gene is the melanoma tumor antigen gene, it might be incorporated into vaccinia viruses in an attempt to immunize patients with melanoma against their unique antigens by raising immune cells with reactivity against their disease.

Dr. Rosenberg discussed initial clinical trials involving the TIL cells that have been used for these gene therapy studies. A cancer nodule is removed and incubated in IL-2 to selectively grow the lymphocytes from that tumor. After four to six weeks, the patient's own lymphocytes have expanded approximately 10,000-fold in culture and are reinfused back into the patient. He reported that a recent pilot study with these TILs in 50 advanced melanoma patients elicited response rates of 38%, in contrast to the results of 21% with LAK/IL-2. In fact, in these early trials, patients who have failed LAK/IL-2 therapy have responded to TIL treatment. He added that they now have better ways to grow the TIL cells and, hopefully, can improve results.

Gene Therapy

These experiences, Dr. Rosenberg stated, led them to consider ways to improve immunotherapy using TILs. His research emphasis is in attempting to generate more effective TILs by introducing foreign genes to improve the antitumor activity of these cells. He emphasized the observation that TILs, once reinjected into the patient, accumulate and home to tumor deposits and increase in number at those sites.

He cited one patient who received TIL cells that were labeled with indium-111 so the TILs' traffic could be followed throughout the body. This patient had about 30 different nodules, both internal and external. After administering indium-111-labeled TIL, the TIL cells accumulated in each of the patient's tumor deposits. The patient underwent a complete regression of all cutaneous nodules and a substantial partial regression of two lesions on the base of the lung over the course of six weeks.

Dr. Rosenberg added that they can image melanoma better with these TILs than with any monoclonal antibody they have studied. They can also demonstrate that TILs accumulate in tumor deposits by actually biopsying them.

The trafficking and accumulating property of the TILs was the critical observation that led to Dr. Rosenberg's gene therapy studies, done in collaboration with Dr. Michael Blaese and Dr. French Anderson at NIH. The idea behind these studies was to use TILs as a vehicle to deliver improved antitumor activity to the tumor site. More specifically, they would attempt to genetically modify these TILs to enable them to produce protein products that might increase their ability to recognize and destroy the tumor.

Dr. Rosenberg stated that the gene therapy studies were conceived in two phases. The first was to insert a bacterial gene that codes for a bacterial protein, a neomycin phosphotransferase, that could make the TILs resistant to an antibiotic so that they could identify them and study their long-term distribution and survival in humans. The real goal, however, was to insert genes that might be used to improve the therapeutic potency of these TILs.

Dr. Rosenberg explained that the genes to improve antitumor activity are injected using a murine retrovirus, which is a modified murine Moloney leukemia virus. The retrovirus has been genetically engineered so that all viral coding sequences have been removed and the neomycin resistance gene inserted. This is a virus that can attach to and insert the gene, but the virus itself cannot replicate.

Dr. Rosenberg stated that because this was the first gene transfer protocol performed in humans, the study underwent extensive review by the Heart Institute, the Cancer Institute, the Gene Therapy Subcommittee of the Recombinant DNA Advisory Committee (RAC) and the full RAC itself, the Biosafety Committee of the NIH, and the Food and Drug Administration (FDA).

Ten patients have now been treated with these gene-marked TILs. Results of the first five patients were published in the *New England Journal of Medicine* about six months ago. The second five patients have been treated, and results have been identical. Dr. Rosenberg attested to the fact that there have been no safety problems related to this use of retroviruses to insert genes into humans. No virus replication has occurred.

Dr. Rosenberg described the procedure. Approximately 10 million cells are isolated from a patient's tumor and grown in culture. Once a few hundred million cells are grown, they insert the gene using transduction techniques and grow the cells in parallel. After a 10,000-fold expansion, both cell types are injected into the patient. Dr. Rosenberg noted that by using Southern blots, they can verify that the gene has been inserted and is expressed.

A nontransduced cell, Dr. Rosenberg continued, will grow well but will die in the antibiotic G418. The transduced cells now bearing this new gene will grow in the presence of this antibiotic because the new gene is capable of inactivating it. Researchers can, therefore, detect transduced cells, a goal of this first study, using very sensitive polymerase chain reaction techniques (PCR), which allow detection of as few as 1 in 100,000 cells.

Dr. Rosenberg related the results of one PCR experiment from the many performed in these patients to illustrate how this approach to gene transfer works. After the new gene was inserted, it could be detected in the patient's peripheral blood cells until day 19. They also biopsied the patient's subcutaneous tumor deposits at day 19, and they could see the transduced cells accumulating in the tumor. They have detected the gene-transduced cells until day 189 in peripheral blood and until day 64 in tumor biopsy deposits, demonstrating that these cells do survive and function. In another example, which was reported in the *New England Journal of Medicine*, Dr. Rosenberg spoke of a woman who underwent a complete regression of all her melanoma and remains disease free at 20 months.

To illustrate this process graphically, Dr. Rosenberg presented slides of tumors before injection of the transferred cells, which showed actively dividing cells and no infiltrating lymphocytes. By three days after injection, the immunohistochemically stained infiltrating lymphocytes could be seen. By 19 days, the tumor deposit was besieged by infiltrating lymphocytes. The hypothesis is that it is these transferred cells that mediate tumor destruction.

Dr. Rosenberg emphasized that these gene marker studies demonstrate that the gene therapy technology is feasible, safe, and practical, and has several implications for treating other diseases. He mentioned hemophilia and severe combined immunodeficiency disease (SCID) as diseases for which this treatment might be viable and commented that, unfortunately, the technology does not now exist for bone marrow transplants.

In an example of other applications of gene therapy, Dr. Rosenberg noted Dr. Blaese's work in attempting to insert the adenosine deaminase (ADA) gene into children with SCID, based on their ADA deficiency. Dr. Blaese and Dr. Anderson have taken two children who have some peripheral lymphocytes, extracted these lymphocytes, stimulated them to divide, inserted a retroviral vector containing the ADA gene, and reinfused the cells into the patients. The children are responding well. Although it is too early to determine long-term benefits, this illustrates the possibilities for this approach.

Dr. Rosenberg returned to his discussion of gene transfer technology to treat cancer and described a study involving a gene that codes for tumor necrosis factor (TNF). TNF has substantial antitumor effects in mouse models, causing regression of skin and liver tumors just six hours after injection. However, extensive TNF studies in humans have not resulted in any antitumor activity. The difference in effectiveness between mice and humans is due to the fact that the mice require 400 micrograms of TNF per kilogram to result in regression of tumors, while humans can only tolerate about 8 micrograms per kilogram.

To enable humans to benefit from larger doses, Dr. Rosenberg explained, they planned to genetically modify the TILs so that they produce large amounts of TNF. Upon administration of the modified TILs, they would accumulate at tumor sites and produce greater than 1,000 micrograms of TNF per kilogram. They have received permission from the review committees to proceed with these experiments. To insert into TILs two genes, TNF and the neomycin resistant selectable gene, the construct would be to use the retroviral LTR to promote the TNF gene, and use the SV40 early promoter to promote the neomycin resistance gene. The transduced cells make about 20 times more TNF, and the selected cells nearly 100 times the normal amount of TNF, than nontransduced cells make, an amount that should exceed the 400 micrograms per kilogram.

A modified protocol has been approved by review committees, one in which patients receive a low number of cells. Dr. Rosenberg cited two patients who have each received 3 billion of these gene-modified cells. Because of restrictions to patients with 90-day life expectancies, the first patients were a 29-year-old woman and a 42-year-old man, both of whom

had failed all conventional and experimental treatments. Gene therapy treatments began in January 1991 and there have been no side effects in the two patients, but it is too early to comment on effectiveness.

A second gene therapy protocol has been submitted and provisionally approved by the NCI Clinical Research Committee. This therapy, Dr. Rosenberg stated, involves the use of gene-modified tumor cells as a potent way to immunize patients against tumors. Dr. Philip Leder showed that IL-4 put into tumor cells makes them more immunogenic, and Drs. Drew Pardol and Eric Fearon demonstrated the same with IL-2. Dr. Rosenberg has shown that insertion of the gene for TNF produces the same results.

Dr. Rosenberg explained that when these genetically modified tumor cells are inserted into animals and produce TNF, they will grow for about 10 days and then spontaneously regress, where the nongene-modified tumor will continue to grow. Human tumors injected into nude mice that produce TNF will also not grow, whereas the untransduced tumor will grow. In animal models, it has been shown that these cytokine-producing tumors will result in the production of very potent killer cells that can then be isolated from these animals.

The proposed protocol, Dr. Rosenberg continued, involves excising tumors from patients, inserting the gene that codes for the cytokines, and using them to immunize patients. Dr. Rosenberg concluded by stating that he expects this to be the next gene therapy protocol.

Questions and Answers

A question was posed regarding why, in the TNF studies, there was less than a twofold difference in production between the selected and the nonselected cells. Dr. Rosenberg replied that as TILs grow, cells with a slight growth advantage will tend to outgrow other TILs in the population. And, even without cloning, TIL populations become very oligoclonal as they grow. He added, in response to a follow-up question, that selective growth advantage of the TNF-modified TIL does occur in some cases, but that he has not seen it in most of his studies.

Another participant asked if Dr. Rosenberg's suspensions for TILs still have LAK cells and if the LAK cells could be damaging to normal cells. Dr. Rosenberg responded that LAK cells can lyse fresh tumor cells, but not fresh normal cells. Since LAK cells grow in culture only up to two to three weeks, the TIL administered to patients, which have grown for four to six weeks, have very few, if any, LAK cells left.

In the patients with TNF-modified cells, a participant asked, is there any systemic TNF in the serum? Dr. Rosenberg commented that he has not detected TNF circulating in these patients, since they have administered only small amounts (3 billion TIL) thus far. The half-life of TNF *in vivo* is only about four minutes, so it will be eliminated very quickly and very large amounts will have to be produced for detection. Patients will be monitored very carefully as doses increase. He added, in response to a related question, that he cannot treat patients with known brain metastases in this protocol, so they have not yet seen impact on brain metastases.

The final question asked about the long-term survival of patients receiving TIL treatments. Dr. Rosenberg emphasized that the LAK/IL-2 protocol is the only one with a long enough follow-up period for which to judge long-term survival. TIL treatment only began in the past year and a half. In the prospective randomized trial comparing LAK/IL-2 with IL-2 alone, there has been a four-year actuarial survival in patients with advanced melanoma and renal cell cancer, the predominant patients which have been treated. It is 33 percent in the LAK/IL-2 group, compared with 21 percent in the IL-2 group. Dr. Rosenberg concluded with the

statement that he would like to exceed that rate with the TIL protocol, but that it is still too early to say.

VI. PROGRESS IN NEOADJUVANT THERAPY—DR. DANIEL IHDE

Dr. Ihde began his presentation by explaining that systemic chemotherapeutic agents are administered to cancer patients in three clinical settings: (1) definitive, or induction chemotherapy; (2) adjuvant, or postoperative chemotherapy; and (3) neoadjuvant chemotherapy, also called primary, preoperative, and induction chemotherapy.

Definitive chemotherapy is the predominant therapy for an advanced cancer for which no other satisfactory treatment exists. Its goal is long-term survival with eradication of the tumor or cure in patients with drug-sensitive neoplasms such as Hodgkin's disease and testicular cancer. Prolongation of survival is the usual result in tumors that are infrequently curable with chemotherapy but are very responsive to it, such as advanced small-cell lung cancer, bulky ovarian cancer, and multiple myeloma. Tumor regression and symptomatic palliation are the usual goals of treatment in modestly responsive tumors, such as nonsmall-cell lung cancer, colon cancer, and malignant melanoma.

Adjuvant chemotherapy is given after successful surgery or irradiation of a localized cancer to reduce the risk of later tumor recurrence. Its goal is long-term survival and cure when administered after definitive irradiation or surgical resection of Hodgkin's disease or testicular cancer, respectively. Since these cancers are very responsive to systemic agents, an equally viable management approach is to administer chemotherapy only as relapse occurs. Prolongation of survival is an achievable goal after surgery—sometimes followed by irradiation—for breast, colon, and rectal cancer. Increased disease-free survival has been documented in randomized trials of adjuvant chemotherapy for osteogenic and soft-tissue sarcomas. Dr. Ihde remarked that a demonstration of improved quality of life in conjunction with improved disease-free survival would sway almost all individuals in favor of adjuvant treatment. He added that adjuvant chemotherapy can be beneficial even if it does not increase survival.

Dr. Ihde defined neoadjuvant chemotherapy as initial treatment with chemotherapy of a localized cancer for which the alternative of locoregional therapy is less than satisfactory. Subsequent treatment with surgery or irradiation is generally intended. Possible advantages of the neoadjuvant approach include the ability to assess the efficacy of chemotherapy and either continue or alter it after locoregional treatment in responding and nonresponding patients, respectively. This type of therapy has the theoretical advantage of providing the earliest possible treatment of metastatic tumors and cancer cells with impending mutation to multidrug resistant status. More obvious benefits of neoadjuvant chemotherapy, Dr. Ihde pointed out, arise from early tumor regression, which could permit surgical resection that would not otherwise be possible; reduce local recurrence; permit radical surgery to be avoided, so-called organ preservation; and increase the effectiveness of subsequent irradiation. Finally, neoadjuvant chemotherapy could lead to improved survival.

Dr. Ihde told the audience that there has been considerable experience with neoadjuvant chemotherapy in locally advanced squamous cell carcinomas of the head and neck. Response rates to neoadjuvant chemotherapy have been much higher than in locally advanced tumors recurring after surgery or irradiation, and some have proven to be durable.

Dr. Ihde presented data from the Dana Farber Cancer Center which plotted actuarial disease-free survival as a function of response to initial treatment with cisplatin, bleomycin, and methotrexate. An estimated 83 percent of patients were free of tumor recurrence at three years.

Other observations in head and neck cancer patients given neoadjuvant chemotherapy are more problematic. Response duration to chemotherapy alone is often short. Although some patients initially judged to be surgically unresectable can be converted to resectable status after chemotherapy, it is not yet clear that local control is improved. A fraction of patients will simply refuse necessary local therapy of their cancer because of dramatic tumor regressions produced by chemotherapy.

Dr. Ihde said that relatively few trials of neoadjuvant chemotherapy in head and neck cancers have been prospective randomized studies. A recent review of response rates in survival in selected uncontrolled and controlled trials reveals that overall (complete plus partial) responses range from approximately 65 to 90 percent in uncontrolled studies, and 35 to 85 percent in controlled studies. Survival in most uncontrolled studies generally is reported to be superior to that observed in historical controls. But in all randomized studies reported to date, patients given neoadjuvant chemotherapy have similar survival to controls receiving only locoregional treatment.

Dr. Waun Ki Hong of the Veterans Administration (VA) laryngeal cancer study group provided Dr. Ihde with data on a large randomized trial to be published in *The New England Journal of Medicine*. Dr. Ihde described this trial in laryngeal cancer patients, which evaluated the ability of neoadjuvant chemotherapy to permit radical surgery to be avoided, allowing preservation of vocal function. More than 330 patients with locally advanced stages three and four tumors were randomized on this trial. After two cycles of chemotherapy, responders underwent histological evaluation and an additional cycle of chemotherapy followed by irradiation. Nonresponders were referred for laryngectomy and irradiation. Complete responses to chemotherapy in the primary tumor site exceeded 30 percent. Of the 166 patients randomized to neoadjuvant chemotherapy, 64 percent have retained their larynx. Results indicate that neoadjuvant or induction chemotherapy and definitive irradiation can be an effective treatment strategy for achieving laryngeal preservation in a high percentage of patients without compromising overall survival.

Dr. Ihde explained that only uncontrolled trials of neoadjuvant therapy of nonsmall-cell lung cancer have been performed. Potential benefits of this treatment are somewhat different than in head and neck cancer. Reducing the risks of local tumor failure is more important in head and neck cancer than in nonsmall-cell lung cancer because resulting symptoms in head and neck cancer are more devastating. Surgical resection is the most effective local regional treatment for lung cancer. Therefore, increasing the frequency of surgical resection is the appropriate goal of neoadjuvant treatment in nonsmall-cell lung cancer. Dr. Ihde provided survival results from a recent randomized study, which demonstrated significantly improved survival when five weeks of cisplatin and vinblastine treatment preceded definitive irradiation of the chest in locally advanced cancers. These results imply that chemotherapy may be sufficiently active in nonsmall-cell lung cancer to be potentially effective in the neoadjuvant as well as other clinical settings.

Next, Dr. Ihde presented information on seven recent North American Phase II studies of neoadjuvant chemotherapy in locoregionally advanced nonsmall-cell lung cancer. These Phase II trials were heterogeneous in most respects. Combination chemotherapy, including cisplatin, was given in all trials, while neoadjuvant treatment included chest irradiation in five of the seven. The number of patients in each study was small, ranging from 22 to 85. Complete plus partial response rates ranged from 44 to 73 percent. The fraction of patients whose tumors could eventually be surgically resected varied between 14 and 88 percent. Absence of viable tumor or pathologic complete response in the surgical specimen was documented in 0 to 32 percent of patients beginning therapy. Chemotherapy response rates appeared much higher than in patients with distant metastatic nonsmall-cell lung cancers. Favorable survival effects were not clearly evident but could have been present.

Dr. Ihde commented that comparisons of uncontrolled trials to institutional historical controls and comparisons among Phase II trials are problematic. Validity is uncertain in comparison of historical controls because staging procedures have become more sophisticated. Thus, current patients with locally advanced cancer may have lesser tumor volume than historical control patients. The relative effectiveness of neoadjuvant regimens used in different uncontrolled Phase II studies is also difficult to compare. In lung cancer, the term *operability* means that thoracotomy can be performed with the expectation of performing curative surgical resection. Markedly heterogeneous and subjective definitions of operability among thoracic surgeons are probably the most important source of variability in tumor extent among patients in various Phase II studies. Patient selection is more stringent in the neoadjuvant trial in which patients must tolerate chest irradiation, combined chemotherapy, and radiotherapy. Due to these difficulties which hinder comparison of uncontrolled studies of neoadjuvant therapy of lung cancer to either historical controls or to each other, controlled trials will often be necessary to prove the efficacy of this approach.

Dr. Ihde stated that a recently opened, intergroup, randomized trial seeks to determine whether initial chemotherapy followed by surgical resection is superior to initial chemotherapy followed by irradiation. He added that an attractive study design would involve preoperative therapy followed by surgery versus definitive chest irradiation in initially inoperable patients. Preoperative therapy followed by surgery versus immediate surgery possibly followed by adjuvant therapy with the same regimen would address whether neoadjuvant treatment offers any advantage over no chemotherapy or adjuvant chemotherapy to inoperable patients. Comparing surgery, alone or with postoperative irradiation, and adjuvant chemotherapy to surgery has the advantage of documenting precise pathologic staging data in all patients. A current intergroup cooperative group trial of this design has just begun to accrue operable patients.

Dr. Ihde revealed that a randomized, controlled, intergroup trial in localized esophageal cancer reported improved survival with the addition of initial 5-fluorouracil and cisplatin to definitive irradiation. This will be the second consecutive year at the spring cancer meetings in which a cooperative group randomized trial showed survival benefit with the addition of chemotherapy to locoregional treatment of esophageal cancer. Dr. Ihde then described two studies that emphasize the potential and possible limitations of neoadjuvant chemotherapy in permitting organ preservation. In one study—an uncontrolled Phase II trial in invasive bladder cancer patients—methotrexate, cisplatin, and vinblastine were added to initial irradiation. At 30 months follow-up, 64 percent of patients had intact bladders. The other study was a retrospective analysis performed in locally advanced breast cancer patients given initial chemoradiotherapy. Some patients then received mastectomy, while others did not. Local recurrence rates were worse in patients who did not undergo mastectomy, except for patients who had clinically complete response to initial treatment.

Dr. Ihde concluded his review of neoadjuvant treatment in head and neck and nonsmall-cell lung cancers. He gave a summary of currently attainable and potential goals of neoadjuvant chemotherapy. An increased likelihood of surgical resection probably results from neoadjuvant treatment in some patients with nonsmall-cell lung, breast, and head and neck cancers; this could be a worthwhile goal in certain advanced tumors of the bladder and uterine cervix. Reduced rates of local recurrence would be valuable in locally extensive tumors of the breast, uterine cervix, head and neck, and esophagus. It is not certain whether such reduced rates occur in patients who do not achieve a complete response to therapy. The most broadly applicable benefit of neoadjuvant chemotherapy at present is reduction in the need for radical surgical procedures. Organ preservation in patients with breast, bladder, head and neck, esophageal, and anal cancers, and osteosarcoma is a reasonable option for those patients who attain a complete response to neoadjuvant treatment. Neoadjuvant treatment has been highly successful in osteosarcoma of the extremities, where limb preservation is currently possible in up to 80

percent of patients. It is highly likely that neoadjuvant chemotherapy improves survival in localized esophageal cancer. In conclusion, Dr. Ihde said that after 10 to 15 years of existence, neoadjuvant chemotherapy remains worthy of continued intensive clinical investigation.

Dr. Calabresi opened the question and answer session about neoadjuvant therapy. A question was asked if it would be more effective to do an organ-saving surgical cytoreduction, followed by chemotherapy and radiation therapy, instead of giving neoadjuvant chemotherapy first. This approach would be more effective because it would not reduce the immune resistance of the patients in the beginning of therapy. Dr. Ihde replied that this is an interesting approach, although he is not aware of a considerable amount of published data concerning this approach. He continued to say that in nonsmall-cell lung cancer—and other cancers as well—debulking surgical procedures have proven unsuccessful and are not commonly performed. It is difficult to evaluate the survival of patients without a randomized control group. In the VA laryngeal cancer study, patients who received chemotherapy as their initial treatment did not appear to have immune dysfunction sufficient to compromise their survival over a 30- to 36-month follow-up.

Dr. Durant asked if there were plans to extend this treatment to stage two, rather than stages three and four, head and neck cancers in which there is a much smaller tumor burden. Dr. Ihde agreed with Dr. Durant's suggestion and answered that he was not aware of any plans sponsored by the NCI to identify and investigate a group of stage two head and neck cancers in conjunction with this approach.

Dr. Ihde mentioned that Dr. Fisher is introducing preoperative chemotherapy in more localized forms of breast cancer and has a randomized trial underway. Dr. Fisher said that preoperative therapy has tremendous biological implications. The basis for using adjuvant chemotherapy began in the 1960s with the work of Howard Skipper and Frank Schabell and their hypotheses related to growth kinetics of micrometastases versus growth of the primary tumor. The hypotheses of Skipper and Schabell have never been tested, but Dr. Fisher feels that they can be tested in this mechanism. It has been demonstrated that release of growth factors occurs with the removal of the primary tumor, which stimulates growth kinetics of metastases, and that the use of chemotherapy or other agents will inhibit the growth stimulation mechanism. Thus, there is reason to give chemotherapy sooner in treatment. For example, Goldie and Coleman talked about the possibility of chemotherapy-resistant clones developing the longer the wait in giving the therapy. On this basis, it was decided to do a trial of preoperative therapy in breast cancer. Dr. Fisher and his group now have 850 patients randomized to receive the locoregional treatment, with chemotherapy given either before or after local therapy. The trial should be completed within 1992 and Dr. Fisher will be able to correlate the response of primary tumor with events in micrometastases. Survival is the main endpoint. Dr. Fisher explained that he has slides that demonstrate tumor shrinkage. For instance, the tumor may shrink like a grape to a raisin, a plum to a prune, or more like a dandelion in which there are little parts left behind. If Dr. Fisher's use of systemic therapy for cancer improves survival, it would be conceivable to move better therapies into the preoperative setting or to eliminate the need for surgery completely for the management of breast cancer.

Dr. Ihde agreed with Dr. Fisher's comments and added that he had heard Dr. Goldie talk about whether chemotherapy should be given before or after surgery. Dr. Goldie used the analogy of people approaching a waterfall in which the people farthest away from the waterfall would receive no benefit. The people who had gone over the waterfall probably would receive no benefit. That is, they would have already developed metastases or other more biologically aggressive tumor. But, the people right at the top of the waterfall might have benefit. The only way to test this hypothesis is by conducting a trial similar to Dr. Fisher's.

Dr. Calabresi announced that he and his group have started a stage two neoadjuvant head and neck cancer study because he and his colleagues have had good results in stages three and

four. Dr. Calabresi's group has seen very dramatic results in certain patients who were unresectable in nonsmall-cell carcinoma of the lung. Some of his patients who were previously unresectable have survived beyond four years. He suggested that there should be more generalized clinical trials in this area.

Dr. Calabresi commented that his group started a protocol on regionally advanced carcinoma of the pancreas with 5-fluorouracil and platinum and preoperative radiation with some success, although there are no conclusions at this time.

Dr. Ihde agreed with Dr. Calabresi and proceeded to say that there have been trials of cisplatin-based chemotherapy in patients without distant metastases in the past six to eight years. Only a few of these trials suggest that there is a modest survival benefit to chemotherapy in nonsmall-cell lung cancer. Dr. Ihde believes that, eventually, available tools could have a modest, but real, effect on survival of these patients with locoregional disease.

Dr. Salmon said that he agreed that all of the early treatment is probably adjuvant treatment. The question of whether treatment should be preoperative or postoperative with small tumors depends on long-term results. However, with the larger tumors, he thinks it is unambiguous for several tumor sites that it does render patients operable who would otherwise not be operable. The degree of responsiveness to neoadjuvant therapy is underestimated.

Dr. Chan asked if biological response modifiers or immunotherapy agents are used in adjuvant therapy. Dr. Ihde responded that he was not aware of published reports that have incorporated biological response modifiers.

VII. OFFICE OF SCIENTIFIC INTEGRITY REGULATIONS— DR. CLYDE WATKINS

Mrs. Bynum reminded the members that questions were raised at the last meeting regarding the disposition of some rather notorious cases of alleged scientific misconduct. She introduced Dr. Clyde Watkins, Acting Deputy Director of the NIH Office of Scientific Integrity (OSI), to present information on how the NIH and the Office handles such matters.

Dr. Watkins began by observing that the OSI is now two years old and that in that time 104 allegations of misconduct have been resolved. He said the Office maintains an active case list of between 60 and 80 cases. This totals less than 200 cases that have been or are being dealt with, including cases being managed directly by the Institutes and those being managed by the OSI. These numbers indicate that allegations of scientific misconduct are rare. However, they still have a large impact in terms of public relations, funding, and confidence in scientific work.

Dr. Watkins explained that the OSI monitors and oversees the responses of universities and research institutions to allegations of misconduct and has the authority to manage cases when warranted. An institution may be involved, directly or indirectly, in a lawsuit, such as a suit for wrongful termination or libel. They may also be involved in a relatively new type of action under which citizens can sue on behalf of the Government to recover funds obtained under false pretenses. These actions are a result of a recent modification of the False Claims Act. These suits are filed under seal, and the defendant is usually an academic institution. Any ongoing OSI investigations in these cases are disrupted, since OSI's inquiries must be suspended until its advice has been given to the Justice Department on whether to join the suit.

While most allegations come from institutions, some come directly from individuals, many of whom—at least at the beginning of the process—wish to remain anonymous. The OSI institutionalizes anonymous allegations by developing issues of science that must be addressed

by a respondent. An initial review determines whether there is any substance to the allegation; this is the primary reason that the Office is staffed almost exclusively by scientists. Many allegations do not make it to the next stage because they clearly lack substance, do not fit within the Public Health Service definition of misconduct, or obviously involve honest error.

Dr. Watkins read the PHS definition of scientific misconduct: "Fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community." The scope of activities encompassed by the phrase "other practices" is the source of some concern in the research community. Dr. Watkins described a gradation of activities from errors in calculation to selective reporting or nonreporting of data, which may involve sloppiness or honest mistakes, to abuses of the peer review system either within the PHS or in journals, which would clearly be wrong. The OSI, he stated, does not try to fit "everything under the sun" into the PHS definition of misconduct.

If there is substance to an allegation, he continued, the OSI notifies the institution that it should conduct its own review and, if necessary, conduct a formal investigation. Only when an institution is in conflict or is unwilling or unable to conduct a thorough and objective review does the OSI take over management of the case. There is a slightly different mechanism for the intramural programs of the PHS, in which the institute or agency conducts the inquiry and then the OSI conducts the investigation in consultation and collaboration with each other.

If misconduct is found to have occurred, sanctions are recommended by the institution and by the OSI relevant to their separate interests, ranging from letters of reprimand, prohibition of service on PHS advisory committees for a period of time, or a requirement that a respondent's research activities be monitored for a specific period. The ultimate sanction is debarment from receiving Federal funds for research activities. If no misconduct is found, the OSI will assist the respondent in restoring any damage to that individual's reputation. While strict confidentiality is observed, there is always some damage as a result of investigations. Information about closed cases is released under the Freedom of Information Act only when there has been a finding of misconduct.

Dr. Watkins said that the OSI recently held a series of three regional symposia with research administrators and university counsel to share experiences with implementing regulations on misconduct. These meetings were successful in establishing the credibility of the OSI, gaining a better understanding of the responsibilities and needs of institutions, and developing a partnership for the handling of scientific misconduct. He argued that the primary responsibility for the policing of science should lie with the institutions, and that the protection of PHS interests should be conducted on a scientific basis. The partnership between OSI and research institutions is essential to this process.

Dr. Watkins noted that many members were probably interested in concerns about due process in OSI procedures and briefly discussed the OSI viewpoint concerning the Abbs case at the University of Wisconsin. Professor James Abbs sued the OSI in the Western District of Wisconsin Federal District Court to enjoin the Office from pursuing an investigation because of his claim that the investigation did not allow for sufficient due process to protect his Constitutional interests in liberty and property. The judge in this case determined that there were no Constitutionally protected interests at risk by an OSI investigation, and so there was no need to further determine whether OSI procedures supply sufficient due process. Dr. Watkins noted that the OSI believes that its procedures do allow adequate due process and regrets the lack of an opportunity in this case to address the question.

Another part of the decision in the Abbs case upheld the challenge that the OSI's policies and procedures should be treated as rules because they affect individuals and the public. The

judge agreed that the policies must go through a period of public comment as part of the rule-making process. The decision on whether to appeal or initiate a public comment procedure has not yet been made. The OSI, Dr. Watkins stated, welcomes the opportunity to receive input from the community on its policies and procedures.

He added that two other suits are being pressed against the OSI and the Department concerning due process; one is in the Eastern District of Wisconsin and one in the Western District of Pennsylvania. At least one of these cases, he added, involves the NCI.

Asked whether there is a time limit on bringing allegations before the OSI, Dr. Watkins answered that there is no statute of limitations and that the Office would prefer that a time limit did exist. In response to a question about false accusations, he stated that allegations brought in bad faith are actionable, adding that bad faith is not a serious problem—of the 168 cases that have been mentioned, the OSI felt that one case involved an allegation brought in bad faith. In most cases, he said, the complainants are not correct in their allegations, but there is enough substance to require further review; in many cases the complainant simply does not have enough accurate information.

Asked for quantitative information on the OSI's caseload, Dr. Watkins reported that about 70 percent of the cases received mature into inquiries and that probably half of those mature into investigations. Perhaps a quarter to a third of those cases that are investigated, he said, result in a finding of misconduct. Of the 104 cases closed so far, 20 to 25 involved findings of misconduct, with various levels of seriousness. Most of the sanctions that have occurred, he said, have been remedial in nature. He could not comment on the involvement of the Justice Department in active cases, but noted that this does not happen often.

Dr. Richard Adamson expressed concern about the staff time, both for the OSI and the institutions, that can be taken up by frivolous and repeated allegations. Dr. Watkins responded that complainants can often be persistent, but that inquiries are not reopened unless additional evidence is made available. He observed that the time taken by frivolous allegations is not extensive, but that there is no alternative to addressing issues that are found to be substantive.

In response to a question concerning the proportion of NIH grants, in terms of dollars or numbers of grants, that have been involved in allegations of scientific misconduct, Dr. Watkins said that he had not done calculations to arrive at such numbers, but suggested that the proper adjective is "rare." He said that the denominator for such a calculation would probably be over 30,000, since it would include all research funded by the Public Health Service; he added that the OSI's jurisdiction extends to false claims or misconduct in the application process as well as within funded projects. He also noted that such calculations would be somewhat misleading in that they could taint entire projects when allegations of misconduct only involve parts of the projects. Dr. Watkins added that the issue of public confidence in science goes beyond the question of any dollar figures involved in the allegations.

Another question involved the costs of OSI investigations to the institutions and to the Federal agencies and whether there are guidelines concerning the timeliness of the investigations. Dr. Watkins explained that Federal regulations require that an inquiry should take 60 days or less and that an investigation, if warranted, should follow within 30 days and take no more than 120 days, so that the entire process should take six to seven months. He added that this is an optimistic goal; the institutions are getting better at meeting these guidelines, he said, and the OSI hopes to improve over time.

The OSI, he stated, does not have all of the facilities it needs at hand; another constraint is the fact that cases managed by the OSI are the most difficult cases. The process is slowed by

the fact that a panel of expert advisors from across the country must be convened for each investigation, and time is required for frequent correspondence with the institutions involved in the cases.

In terms of costs, institutions are reporting expenditures up to $30,000 for the entire process of going through an inquiry and an investigation. The budget of the OSI, he added, is roughly $1.6 million.

Dr. Calabresi suggested that the OSI consider publishing information in a prominent journal to demonstrate what is being done about scientific misconduct and to show that the number of cases is relatively small. Dr. Watkins said that the OSI is looking into ways of doing studies on subjects such as the effects of the process on "whistle-blowers" and the effects of being a respondent on a scientist's career. The most important area to be explored, he ventured, is the development of case law to define "other practices" and clarify the consequences of misconduct.

VIII. REMARKS BY THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH—DR. BERNADINE HEALY

Dr. Broder began his introduction of Dr. Bernadine Healy by announcing that she was confirmed as Director of the National Institutes of Health on March 22, 1991. He asserted that her appointment is propitious given the new commitment of NIH to study diseases that limit the survival and quality of life of women, voicing his belief that such research can only be effectively done when women are fully represented in the biomedical sciences.

Dr. Broder quoted Dr. Richard Ross, who was Dean of the Johns Hopkins School of Medicine when Dr. Healy was an intern there, as having stated that "If a training program were to be designed for an individual to be an NIH Director, one would find that Dr. Healy's background would typify it." Her experience covers clinical practice, research, large clinical trials, administrative responsibilities in policy development at the White House, and the creation of a superb research program at the Research Institute of the Cleveland Clinic Foundation.

In a sense, he noted, this appearance is a homecoming for Dr. Healy, who met with the NCAB as an ex-officio member from 1984 to 1986 while serving as Deputy Director of the White House Office of Science. During that time she reviewed many of the plans for programs now reaching maturity, such as studies of the molecular biology of cancer, the earliest AIDS research, and the evolution of the Cancer Information Service (CIS).

Dr. Healy thanked Dr. Broder for his assistance during the transitional phase of assuming her new position. She stressed the importance of being able to learn the interests and concerns of the Board firsthand from its members and to share her thoughts about the priorities and principles she hopes will guide the NIH in the years ahead.

Dr. Healy asserted that the first priority of the NIH is its human talent base. The quality of our science, she said, is no better than the quality of the scientists we support. The number of scientists receiving some level of NIH support, she added, is conservatively estimated to be about 50,000. There are at least four general areas in that context that need our attention.

The first is that we ensure an environment for opportunity. Dr. Healy asserted that, in addition to providing research training, the excitement of research must be communicated to the young and an environment where excellence is supported must be created. As the heart of our merit-based investment mechanism, the peer review system must be kept vital and above reproach.

Another factor in sustaining the talent base is the intelligent allocation of financial resources. It doesn't matter how much money we have, Dr. Healy observed, if we don't invest it wisely. Demonstration of a reasonable degree of financial stability is critical. Dr. Healy said that she has given top priority to formulating specific proposals to make NIH mechanisms more effective; for 1992, she said, the NIH is trying to move the success rate for applicants from approximately 25 percent to 30 percent. She noted that, when superb scientists are in danger of faltering because they barely missed a 25 percent cutoff, there is a perceived crisis for them and for their institutions.

Dr. Healy reminded Board members that in 1991, for the first time, crisis funds have been allocated to the NIH Director. She has directed most of that crisis money to a new research award named after Dr. James A. Shannon, who served as Director during what some have called the golden years of the NIH. These new awards are specifically designed for investigators whose proposals have been judged as highly meritorious by study sections, but would receive no support because their priority scores fall just outside the individual Institute's funding cutoff line. She asserted that, in many cases, the quality of these applications is not statistically different from the quality of those that are funded just on the other side of the pay line. The naming of the award for Dr. Shannon is intended to make a very strong statement that the award is a recognition of individual careers and highly innovative projects, and the award itself will be a statement that the NIH intends to invest in them even if resources are not available to fully support them in this particular year; it is designed to sustain investigators so that they can refine their ideas, address relevant concerns, and, hopefully, come back with a clearly competitive project.

The Shannon awards will provide up to $100,000, including indirect costs, which could be used over a period of up to two years with no more than $50,000 to be spent in one year; some awards will be made for only one year. Indirect costs will be paid at a maximum of 20 percent. NIH staff members will nominate Shannon awardees after peer review has been done.

Dr. Healy stated that the NIH hopes to assemble approximately $30 million for this program and to award between 300 and 500 awards. Funds will be derived in part from the Director's Discretionary Fund; $16 million will come from the newly authorized Transfer Authority. The Shannon awards will not be counted as grants in the calculation of funding success rates.

Dr. Healy turned to a discussion of other long-range issues in financial management. The NIH is embarking on Phase II of cost management even as Phase I is being implemented. A senior-level working group has been assembled to address the issue of indirect costs, composed of Kevin Moley, the DHHS Assistant Secretary for Management and Budget, the DHHS Inspector General, Mr. Kusserow, and the NIH Director. Within the NIH, a team has also been assembled which includes Mr. John Mahoney, Associate Director for Administration; Dr. John Diggs, Deputy Director for Extramural Affairs; and Dr. Jay Moskowitz, Associate Director for Science Policy and Legislation. These two groups bring together important negotiators, budgeters, and payers to take a systemic look at indirect costs.

A second major priority discussed by Dr. Healy, in addition to the talent base, was the public factor. She stated that the NIH must be a leader in the area of public trust, not only through aggressive promotion of scientific integrity, but also in setting attainable research priorities that are in the interest of the public, that are understood by the public, and that are bought into by the public.

Dr. Healy expressed the belief that the Women's Health Initiative mentioned earlier by Dr. Broder is one of those activities that is in the public interest and is an example of an area in

which the NIH has tried to improve its sensitivity to what has been asked for by the public. She noted that the initiation of this project, the establishment of the Office of Research on Women's Health, temporarily headed by Dr. Ruth Kirschstein, and the leadership of the Directors of the various Institutes demonstrate a substantial commitment to addressing the major health problems of women, including cancer, cardiovascular diseases, and osteoporosis.

Dr. Healy observed that while women have an advantage over men in terms of longevity, a price is paid when many women spend substantial portions of their lives in frailty, isolation, and poor health. There is much evidence, she said, that the quality of life for women is not what it should be. The Women's Health Initiative will investigate the scientific underpinnings of a variety of interventions, such as diet modification, diet supplements, calcium, vitamins, hormone replacement therapy, and smoking cessation, as well as the interaction of these interventions.

The study, Dr. Healy explained, will probably have three components: a large prospective surveillance program; a nationally-based community prevention and intervention study which will look at differences in cultures and differences in socioeconomic strata; and a randomized clinical trial. The planning for this study—the largest of its kind ever undertaken in the United States, if not the world—should be completed or almost completed within calendar year 1991. Dr. Broder, Dr. Peter Greenwald, and others at the NCI have been leaders in the planning process. The cost of the project could be as much as a half billion dollars over the next 10 years.

Another high-priority area, Dr. Healy continued, is minority health. A number of important minority health issues will be addressed in the Women's Health Initiative. Other dimensions of minority health are being addressed within the Institutes, focusing on the diversity of health differences related to problems such as AIDS, diabetes, hypertension, cancer of various organs, and kidney disease. The NIH has a newly established Office of Minority Affairs headed by Dr. John Ruffin, who is working hard to develop a trans-NIH agenda to attack minority health research.

Technology transfer, Dr. Healy added, is another high priority. One mechanism for transferring the discoveries of the laboratory into prevention, diagnosis, and treatment is partnership with industry. She stated that the NIH is the leader among Federal scientific agencies in the number and types of linkages it has established with industry and the creative ways in which it has used them.

In closing, Dr. Healy discussed the importance of placing medical research in the context of the public that supports it, arguing that the success of American science in general is owed largely to its having developed in a nonpolitical way and to the fact that virtually every person in the country has been touched by the successes that have come out of "the national treasure called the NIH." She emphasized that the NIH must learn from its successes to avoid allowing its scientific pursuits to be disassociated from the concerns of society in those cases where biomedical research occasionally encounters conflict. She cited institutional review boards for the protection of human subjects, animal care committees, and the recent endeavors to address ethical concerns on the part of the human genome research program as examples of leadership in addressing the concerns of society.

Mrs. Brinker asked Dr. Healy what the NCI should communicate to the American public about its charter, its progress, or its challenges for the future. Dr. Healy answered that on one level, it is important to communicate what the Institute has done for the individual and specific problems that confront people. At a broader level, moving away from specific diseases, she stressed the importance of not allowing the public to take the NIH for granted.

Dr. Howard Temin asked how Dr. Healy deals with two questions relating to the NIH's successes: first, the issue of the inflated cost of medical care resulting from success in medical research; and secondly, the increased pool of investigators that exacerbates the funding crunch. In responding to the first question, Dr. Healy referred to an article by Dan Greenberg suggesting satirically that the way to reduce health care costs is to offer 1950s care at 1950s prices; the public, she said, would not be willing to accept that kind of bargain. In terms of the second question, she acknowledged the fact that science defies the law of supply and demand. She compared the 1982 research project grant portfolio of about 16,000 grants with the projected 1992 portfolio of 21,000 grants and concluded that this does not represent extraordinary growth given the advances in science during the past 10 years.

IX. INNOVATIVE MECHANISMS TO INCREASE INVESTIGATOR-INITIATED CLINICAL RESEARCH—DR. MARVIN KALT AND DR. MICHAEL FRIEDMAN

Dr. Marvin Kalt, Deputy Director of the Division of Extramural Activities, began by noting that at its last meeting, members of the Board expressed interest in being kept informed about progress being made to stimulate the development of high-quality, innovative, clinical research proposals. He stated that the DEA has been working closely with the Cancer Therapy Evaluation Program and the Cancer Centers Program to optimize the referral and review resources available to evaluate clinical research applications. The DEA has tried to broaden the selection of reviewers and the utility of summary statements in conveying to applicants where their ideas stand in relation to the state-of-the-art in their fields. The Institute has endeavored to add to the experimental therapeutics (ET-2) study section reviewers with experience and qualifications to evaluate applications covering the full spectrum of clinical investigations. He announced that three such candidates have been nominated to the ET-2 study section and will begin their terms on July 1st.

The Division of Research Grants, he added, has stated that it will continue to add relevant reviewers as the application load dictates, and, when a sufficient level of clinical applications can be sustained, will consider developing a fully dedicated clinical study section. Similar procedures are under way in the prevention and control area. NCI staff have forwarded the names of potential reviewers with clinical expertise for consideration as members of the NIH reviewers reserve. Membership in the reviewers reserve allows an individual to serve as a full voting member on any chartered initial review group within the Public Health Service. Dr. Kalt also reported that the NCI will issue over the next year a number of new Requests for Applications (RFAs) on specific topics in areas of high priority for clinical research.

Dr. Kalt noted that the formation of standing review groups cannot be justified if applications are not coming in in sufficient numbers. He urged potential applicants not to be deterred by the odds. Investigators can assure that quality applications arrive at study sections through critical self-review and prescreening of applications by colleagues. Dr. Kalt noted that researchers can gain instruction through the review process and focus their efforts by reading summary statements on both successful and unsuccessful applications.

Dr. Kalt introduced Dr. Michael Friedman, Associate Director of the Cancer Therapy Evaluation Program, who described some of that Program's specific activities. He called the members' attention to a program announcement in their notebooks that expresses the need for applications for clinical therapeutic research. Applications can represent a single institution or multiple institutions.

The announcement carefully states that all kinds of activities are within the Program's scope. It emphasizes, in addition to systemic modalities such as drugs, the need for innovative

clinical trials concerning radiation therapy, surgery, and combinations of all of these. Although the announcement is not aimed singularly at the ET-2 study section, it is hoped that all grants that are appropriate will be reviewed there, and that the ET-2 study section will return to its original charge of reviewing and evaluating clinical investigations.

Dr. Friedman observed that in addition to quantity, the quality of applications is a concern. One way to address this problem, he noted, is the education session that will be held at the upcoming cancer meetings in Houston. This is a joint effort among the CTEP, the Cancer Centers Program, others within the Division of Cancer Treatment, and the Division of Research Grants. The session, to be held on May 19th between 1:00 and 3:15 pm, is entitled "How to Prepare a Successful Clinical Research Grant Application." This type of session will be an ongoing activity. Dr. Friedman added that counseling and assistance will be offered to applicants in preparing second and third applications until success can be achieved.

Dr. Friedman also said that an upcoming issue of the *Journal of the National Cancer Institute* will contain a number of papers on this issue, including a report by Dr. Emil J. Freireich on his interviews with researchers at major cancer centers on how to foster clinical research and support the careers of young investigators.

Asked why the mechanism used was a program announcement instead of an RFA, Dr. Friedman answered that there is an ongoing concern that the NCI runs the danger of having too much of the portfolio committed with dollars targeted for specific activities. Before setting aside money, it was decided to experiment with accomplishing the goal more flexibly through a program announcement. It may be necessary to conclude later that this was not as successful as setting aside money.

Another reservation is that using an RFA focuses applicants on a certain kind of research, whereas the goal in this effort is to stimulate applications broadly, including all disciplines, with the only common thread being the intent of therapeutic outcome. They can be purely clinical studies or, more likely, laboratory studies correlated with clinical activities. Large, definitive trials are less likely than pilot innovative studies. The range of possibilities is so great that planners were reluctant to limit visions initially.

A third consideration is the need to make this an ongoing activity. Dr. Friedman argued that unless the ET-2 study section can be presented with round after round of large numbers of applications, it will never be able to return to its original format and will continue to be a diverse body handling the overflow.

Dr. Broder agreed with Dr. Friedman and compared the RFA mechanism to a jumper cable, arguing that it is better in this case to have a battery that works. This means having in place a chartered, standing study section, so that when a pay line is set, clinical research that is judged superior to that pay line will be funded. He emphasized, as Dr. Friedman emphasized earlier in his presentation, that no criticism of the membership of the ET-2 study section has been implied.

A member asked for a history of the ET-1 and ET-2 study sections. Dr. Friedman explained that, of the two experimental therapeutic study sections, the ET-1 was dedicated to more basic pursuits and ET-2 was originally chartered to be more of a clinical investigation review committee. As the number of clinical applications proved to be small, the study section was asked to take over the overflow from other study sections. However, the original charter still stands.

Dr. John Laszlo, Senior Vice President for Public Affairs, American Cancer Society in Atlanta, Georgia, commented that organizing a clinical review committee will present a problem in dealing with the technology used for clinical research; a panel would have to have experts in all of these technologies in addition to those with experience in clinical trials. He also raised the problem of the definition of clinical research and noted that the Institute of Medicine is embarking on a project concerned with defining clinical research and fostering training in this area. Finally, he asked what percentage of the NCI's current portfolio is clinical research.

Dr. Friedman said that the NCI is looking for applications to conduct clinical therapeutic studies of neoplastic disease in human subjects; clinical studies are defined for this purpose as those that involve a clinician/patient interaction with a therapeutic intent. It recognizes all disciplines. In terms of dollar figures, he suggested that clinical research represents about $20 million overall in grants, a substantial but shrinking pool of P01 activities, a small contract activity, and the Clinical Cooperative Group major therapeutic studies of under $60 million. He estimated the total to be about 10 to 12 percent. Dr. Broder pointed out that Dr. Friedman was speaking only about the issue of therapy and that similar efforts to increase applications for clinical research would be made in the areas of prevention and control, diagnosis, and epidemiology.

X. TAXOL: AN UPDATE—DR. BRUCE CHABNER

Background

Dr. Chabner discussed the current status of taxol as an update of his presentation at the February 1991 Board meeting. He reminded the audience that taxol is a plant product extracted from the bark of the pacific yew (*Taxus brevifolia*). Taxol is difficult to synthesize because of its complex organic structure—there are 11 optically active centers in the molecule. Precursors of taxol are found in the leaves or needles of this plant and potentially could be modified to form the whole molecule. Dr. Chabner explained that taxol is particularly interesting to the National Cancer Institute because it represents a prototype for developing natural products as sources for new drugs.

Dr. Chabner further explained that taxol is unique in that it promotes the assembly of microtubules, as opposed to the vinca alkaloids used in the clinic which inhibit the formation of microtubules. Also, taxol stabilizes formed microtubules and prevents their depolymerization. Dr. Chabner reported that antitumor activity was noted in Phase I trials of the drug in patients with melanoma, lung cancer, ovarian cancer, leukemia, and tumors of unknown primary site. There was confirmed activity in ovarian cancer during the Phase II portion of taxol testing. Three studies have shown a response rate of between 25 and 35 percent in patients who are refractory to, or were previously treated with, platinum. Most of the patients are clinically refractory to further platinum therapy. Among the failed platinum patients, a few patients had complete responses. This treatment yielded a higher percentage of responses than any other known therapy. Dr. Chabner cautioned that procuring sufficient amounts of taxol for clinical experimentation and marketing is a major obstacle to further development of this drug.

Clinical Trials

Dr. Chabner noted that since his last presentation, several clinical trials were completed. The Ovarian Cancer Section of the Medicine Branch recently completed a trial in the clinical center that studied the interaction of taxol with Granulocyte Colony Stimulating Factor (G-CSF) as a rescue agent. G-CSF produces increases in myeloid differentiation and hastens the recovery of bone marrow after treatment with a variety of cytotoxic drugs. The purpose of the trial was to determine whether G-CSF could be used with taxol to prevent myelosuppression, which is dose

limiting in patients who receive repeated cycles of therapy. Platinum-refractory patients with advanced stage ovarian cancer were studied. The dose escalation pattern was followed in successive groups of patients up to a total dose of 300 milligrams per meter square. At this dose, G-CSF was successful at controlling bone marrow toxicity. Peripheral neuropathy was the dose-limiting factor. G-CSF was used to rescue from bone marrow toxicity and cycles were repeated every three weeks. In conjunction with G-CSF, the maximum tolerated dose was 300 milligrams per meter square. As a result, a dose of 250 milligrams per meter square was recommended for Phase II. Without G-CSF, the taxol dose must be lowered from 250 milligrams per meter square at the initial cycle to subsequent doses of 130 to 150 milligrams per meter square. Of the 15 patients evaluable for response, there was one complete response and four partial responses, for a 33 percent response rate. In addition, five patients showed less than 50 percent responses and only five patients showed progression during multiple cycles of therapy. Thus far, 14 patients have been entered for further evaluation in the Phase II setting. Results indicate that taxol can be used in higher doses with G-CSF and with a promising response rate.

Dr. Chabner then reported results from a Phase II study of breast cancer patients at M.D. Anderson who had failed primary therapy. The schedule began with the same dose that was used in the ovarian trial but had to be decreased in subsequent cycles because of myelosuppression. Of the 25 stage four patients in this trial, there were three complete responses and nine partial responses, for an overall response rate of 48 percent. The dose-limiting toxicity was myelosuppression and mild peripheral neuropathy was present. Generally, the drug was tolerated well and the responses were beneficial both in terms of tumor progression and quality of life. Dr. Chabner mentioned that as a result of this trial, studies are expanding in breast cancer to confirm this activity and to explore the use of taxol with adriamycin in combination trials.

Dr. Chabner stated that the NCI believes taxol and adriamycin are probably the most active drugs, although data for taxol are limited. Dr. Chabner noted that a trial has begun at the Medicine Branch combining these two drugs. He commented that the NCI feels it is important to explore the combined use of taxol and adriamycin. These two drugs have an overlapping toxicity of marrow suppression that could be ameliorated by using G-CSF with the combination. Results of this trial are not yet available.

A number of Phase II trials, Dr. Chabner announced, are ongoing in the Cancer Therapy Evaluation Program for several diseases, such as gastrointestinal cancer and lung cancer. In addition, there is a study of taxol with cisplatin versus cytoxan in the Gynecologic Oncology Group.

Taxol Supply

Dr. Chabner discussed the problem of increasing the supply of taxol. Since the supply will be inadequate as long as it is obtained from trees, semisynthesis or total synthesis of the drug is being researched. Dr. Chabner remarked that there has been significant progress in the synthesis of taxol. Promising results have been achieved in the synthesis of the taxane ring system, which is a key obstacle for taxol synthesis. Plant hedging has been suggested to alleviate demand for the drug, since numerous species of *Taxus* are pruned and hedged each spring. The University of Mississippi has evidence that there is taxol content in the clippings of commercial yew trees and that these clippings may be used as a commercial source. More speculative work includes hydroponic cultivation or even genetic engineering.

Dr. Chabner stated that as a result of a workshop to discuss ways of obtaining taxol through synthesis or from natural sources, a Request for Application was issued late last year.

A total of 61 proposals were received including topics such as tissue culture, plant genetics, biosynthesis, chemical synthesis, or semisynthesis. Depending on the availability of funds, there are plans to fund at least 10 of these grants.

Summarizing some of the problems with obtaining taxol, Dr. Chabner noted that, currently, the pacific yew is the major source of taxol. This tree is prevalent in the Pacific Northwest where there are many political issues concerning the preservation of the habitat for the spotted owl and the preservation of the forests themselves. Dr. Chabner explained that to obtain taxol, one must cut down the tree and strip the bark. It has been suggested that the drug could be obtained from the needles or leaves of the plant, but the leaf content of plants in the wild is much less than the bark. A Collaborative Research and Development Agreement (CRADA) was negotiated and signed in January of 1991 with Bristol-Myers/Squibb to develop the drug. Bristol-Myers/Squibb, the NCI, and the U. S. Department of Agriculture (USDA) have undertaken a broad procurement of yew trees through forest clear-cutting operations, primarily in the Northwest. Also, the NCI, the USDA, and the University of Mississippi have undertaken the collection of needles and stems from commercial nurseries in the United States. Dr. Chabner feels that commercial plants may become an alternative resource for taxol. An extensive search is being conducted for taxol content in needles from stands of trees in Canada, the Gaspé Peninsula, the Himalayas, and the Soviet Union.

In recent weeks, the USDA and Bristol-Myers/Squibb have been negotiating the harvest of yew trees on Federal lands controlled by the USDA. Bristol-Myers/Squibb has proposed to provide support for a nationwide inventory of yew trees in the national forests, and the USDA would provide Bristol-Myers/Squibb with samples of bark and needles from various forests for analysis of taxol content. Dr. Chabner commented that the agreement would probably be signed in May.

Environmental opposition, Dr. Chabner explained, to clear-cutting operations, which is the most efficient way of harvesting lumber and yew, stems from the desire not to destroy the natural habitat of a number of species, including the spotted owl, and to prevent the erosion of the land on which these trees are found. Local opposition to yew tree harvesting has coalesced in Oregon. There are environmental organizations that are protesting the harvesting of the yew trees and accusing those involved in taxol harvesting with creating a veil of secrecy around the process. Dr. Chabner said that each step of the development process was made public at both the National Cancer Advisory Board meeting and at the meetings of the Board of Scientific Counselors of the Cancer Institute, yet the environmentalists are not satisfied with what they have heard and are attempting to block the harvesting of the yew trees.

Decisions are pending in two cases being heard in Federal courts to block clear-cut harvesting of the National forest in the Pacific Northwest. One case involves sequestering millions of acres of land as a habitat for endangered species and the other would specifically block clear cutting. Dr. Chabner explained that the USDA gave a summary of the taxol procurement situation to the judge. Hoping to arrange an open meeting on the taxol predicament, NCI contacted the Environmental Defense Fund (EDF) in Washington. Thus far, there are indications that the EDF and Bristol-Myers/Squibb are willing to discuss the issues and, perhaps, marshall public support for obtaining access to the yew tree.

Due to immense interest in taxol as a treatment for ovarian cancer, Dr. Chabner announced that there have been many requests to consider patients for treatment. The NCI has responded to these requests by establishing a treatment referral center run by the Cancer Therapy Evaluation Program. This telephone referral center provides information on taxol trials, alternatives for treatment of ovarian cancer, and available drugs (such as the recently approved hexamethylmelamine and other combinations that have shown some activity in patients that have

failed cisplatin and chemotherapy). It also provides referrals to Clinical or Comprehensive Cancer Center protocols.

Dr. Chabner concluded his presentation by reporting that Bristol-Myers/Squibb has collected approximately 25 percent of the anticipated amount needed from this harvest season to have a sufficient supply of taxol for experimental use and some compassionate use. If plans proceed on schedule, taxol will be used for compassionate use as early as July of 1991. Bristol-Myers/Squibb committed through the CRADA to provide 1 kilogram of taxol for compassionate use this year. Patient eligibility will be decided at the individual Cancer Centers.

Asked if the nature of the Bristol-Myers/Squibb agreement is likely to inhibit other companies from getting involved in taxol development, Dr. Chabner answered that the agreement is an exclusive CRADA. He added that Bristol-Myers/Squibb does not have patent rights on the compound and that they receive, under the CRADA, the clinical data. Dr. Chabner expressed his satisfaction with the agreement and said that if the supply problem can be solved, taxol will be a valuable product for Bristol-Myers/Squibb. Dr. Broder interjected by saying that the NCI is trying to encourage competition in the realm of taxol-like drugs. Representatives of the NCI have encouraged the French company Rhone-Polanc to proceed with development in any way possible. Rhone-Polanc manufactures a related drug called taxotere. The NCI also offered its resources and its willingness to collaborate with them.

Dr. Broder continued to say there is a certain knowledge that taxol works. Because it is known that the drug will be active in a subset of women with refractory ovarian cancer, and perhaps other cancers, the NCI feels the need to provide treatment on a compassionate basis to women who have failed other treatments. In the short run, the NCI will face many challenges, but in the long run, the Institute will stimulate competition to develop synthetic taxol and taxol-like congeners. Dr. Broder said that he thinks, in time, renewable resources or synthetic sources will be available. He also stated that short-term emergencies must be addressed, such as the fact that 12,500 women die of ovarian cancer each year.

Dr. Calabresi questioned the use of taxol for trypanosomiasis because the drug had had an effect in an animal model and *in vitro* against the trypanosomes. Dr. Chabner replied that he was not aware that taxol had any activity, except on neoplastic diseases, and if taxol were used against trypanosomiasis, it would aggravate the taxol supply problem. Dr. Chabner thanked the staff of the Developmental Therapeutics Program for their hard work and devotion.

Dr. Salmon suggested that a more environmentally sound approach to harvesting would be to just take out the yew trees rather than clear cutting. Dr. Chabner responded by saying that this has been a suggestion, but it is considered an inefficient way of harvesting trees and this approach would escalate costs tremendously. Dr. Salmon's suggestion is being considered an option in Idaho, British Columbia, and the Gaspé Peninsula, where yew trees grow densely. Dr. Chabner elaborated that the environmentalists want taxol developers only to use needles and twigs or to selectively harvest the yew. He stated that these are impractical alternatives and that the current rate of supply would not endanger the yew tree.

Dr. Bragg asked about the tenure of the responses from taxol in ovarian and breast cancer. Dr. Chabner answered that many have been greater than six months and, in his personal experience, some patients have responded for about a year. There have been longer responses among patients treated at Johns Hopkins and Einstein, but most responses are 6 to 12 months in duration.

Dr. Temin queried about the patent on taxol. Dr. Chabner explained that there is not a patent on taxol, but a company who decides to work on its development will have access to the necessary data to support a New Drug Application (NDA).

Dr. Olden asked if the binding site for taxol has been characterized and, if not, if there are investigations under way. Although grantees are working on this topic, Dr. Chabner replied that it had not been characterized.

Dr. Chan questioned the fate of taxol. Dr. Chabner answered that the drug is largely metabolized. More detailed studies of pharmacokinetics will be conducted when a radioactive drug is available so that researchers can study how taxol is metabolized. Recycling taxol for laboratory use is impossible because less than 5 percent of the dose is found in the urine. Dr. Calabresi added that more of the drug is probably excreted in the bile than the urine. Dr. Chan also asked if taxol had been used intraperitoneally, which could reduce its dose. Dr. Chabner said that a trial is being conducted at Memorial Hospital which is examining intraperitoneal taxol with no results thus far.

XI. IMPLEMENTATION OF THE FEDERAL TECHNOLOGY TRANSFER ACT—DR. THOMAS MAYS

Dr. Adamson introduced Dr. Thomas Mays, who heads the NCI's Office of Technology Development (OTD) within the Office of the Director. Dr. Mays has directed a research program within a biotechnology firm and worked as a patent examiner with the United States Patent and Trademark Office. In addition, he has just completed his work on a law degree.

Dr. Mays began with a review of the history of the country's current balance of trade deficits, which first appeared in the 1970s. At the same time, he said, the philosophy that government could be made more efficient, particularly by looking to the private sector, began to develop. These forces resulted in the enactment of statutes entitled the Stevenson-Wydler Technology Innovation Act, which placed upon Government scientists and engineers the duty to assist in technology transfer. In 1986 this act was amended and renamed the Federal Technology Transfer Act, or FTTA.

The FTTA gave to Government laboratories the ability to enter into Collaborative Research and Development Agreements (CRADAs) with private companies, such as the NCI's CRADA with Bristol-Myers/Squibb to promote taxol production. Another mechanism involves specific rewards that can be made available to Government scientists and other personnel. Under the FTTA, at least 15 percent of the royalties that come from licensed inventions go directly to the scientist inventors. Previously, all royalties flowed directly into the United States Treasury. Additionally, if agencies are not inclined to protect the rights to specific inventions, the FTTA obligates the agency to give those rights to the inventors.

Dr. Mays presented slides that illustrated the implementation of the FTTA within the NIH; he pointed out that the Institute's implementation of the Act is coordinated with other research agencies within the Public Health Service, including Alcohol, Drug Abuse and Mental Health Administration, the FDA, and the Centers for Disease Control. The NIH Patent Policy Board recommends NIH policy; the Office of Technology Transfer (OTT), previously called the Office of Invention Development, implements and coordinates policy for technology transfer.

Each Institute, he continued, has a Technology Development Coordinator (TDC); Dr. Mays fills this role for the NCI. He noted that each Institute differs in how it uses its TDC and that some are not as far along as the NCI in developing technology transfer programs.

Dr. Mays noted that the NIH has an Office of Medical Applications of Research that is involved in developing consensus treatments and making clinical applications available; he stated, however, that his discussion would be limited to patenting and licensing, the primary focus for implementing transfer of technology under the FTTA. The Code of Federal Regulations requires every DHHS employee to report all inventions developed as part of their official duties or during work time. The Institute is then able to evaluate the inventions to determine whether it would be worthwhile to secure a patent.

At the NCI this decision is determined by the Division Director, and the invention report is passed on to the OTD for further processing. The Office plans to develop the ability to provide a patentability report to provide the Scientific Research Director with more information. Presently, however, the Office sends the employee's invention report to the OTT's patent branch, and a contractor's patent attorney prepares and files applications with the Patent and Trademark Office.

The NCI is considering asking the NIH to authorize the Institute to more closely monitor and manage its prosecution of patent applications to reduce costs. Last year, the NCI spent about $500,000 on U.S. patent filings and one million dollars on foreign filings. The new authorization being sought would also enable the NCI to better manage its unique programs such as the Natural Product Screening Program and the Government-owned laboratories in Frederick, Maryland.

Dr. Mays presented a slide representing patent applications filed by the NIH and the NCI. Last year the NIH filed about 220 and the NCI 82 applications, or about 28 percent of the NIH patent portfolio. While the graph shows that growth is in a stationary phase at the present time, Dr. Mays expressed the belief that the curve is going to begin taking off as word gets out that the NIH is serious about patenting.

Dr. Mays explained that there are two ways of licensing a U.S. file application. Currently, the National Technical Information Service (NTIS), an agency of the Commerce Department, is licensing most of the patent applications from the PHS. The OTT is in the process of assuming some of those duties, and already licenses U.S. applications filed from a CRADA. Historically, PHS patent applications have been split into two groups—foreign and domestic applications. With the contracts resulting from the most recent Requests for Proposals (RFPs), these filings will be consolidated—that is, the same attorney will handle both filings.

Concerning costs, Dr. Mays observed that in the experience of universities, it has been estimated that it takes approximately 7 to 10 years before a licensing or technology transfer office is self-sustaining through the receipt of royalties. While the law requires that 15 percent of all royalties must go to the inventor, NIH policy is that inventors will receive 25 percent of the first $50,000 in royalties, 20 percent of the second $50,000, and 15 percent of any royalties over $100,000.

Dr. Mays moved on to a brief overview of the CRADA process. A scientist, working with a potential collaborator or a requestor of materials, will set forth the beginnings of a research plan. When both parties are ready to move forward, the plan moves to the OTD, which will initiate legal negotiations to ensure that agreements conform to NIH policy as well the NCI's goals. The CRADA is then sent through the approval process to the Division Director and then to the NIH Patent Policy Board's CRADA Subcommittee. If approved, the CRADA moves to the NIH Director's Office. Dr. Philip Chen, Associate Director for Intramural Affairs, would sign off on the plan and return it to the NCI Director. The NCI Director can legally sign off on a CRADA, but the NIH Director has a 30-day period in which to exercise a veto.

Presently, the NIH has over 150 CRADAs; the NCI has 30 active and 35 pending CRADAs. Dr. Mays presented a review of the number of CRADAs and their face value to show that some money does flow into support research in the Institutes. In keeping with the spirit of the law, NCI, in the last year, has had approximately 28 percent of its CRADAs with small businesses, and 93 of those are for domestic manufacture. All Divisions of the NCI except DCPC have CRADAs, including the Office of the Director.

Dr. Mays listed some of the companies with which the NCI has CRADAs. He noted that the CRADA with Bristol-Myers/Squibb is unique in that it involves a clinical trial. Since patent protection is not involved, some have asked what the company gets from the CRADA. Dr. Mays pointed out that the company gets exclusive use of the clinical trial data.

In closing, Dr. Mays mentioned the Material Transfer Agreements associated with the Natural Products Division. The NCI has a contract, sometimes inaccurately referred to as a letter of intent, with the government of Madagascar for exploring and retrieving samples of marine and plant materials as part of a natural products screening process.

Asked whether a CRADA is limited to just one year, Dr. Mays replied that a CRADA is a contractual agreement that can be for any specified period of time. He added that the Government can provide anything in terms of personnel, equipment, and supplies, but cannot provide funding, to prevent a sole source contractual agreement; the partner can provide anything, including funding. Dr. Broder added that, as a matter of policy, the NCI would not accept a CRADA in which the partner did not make any contribution except money. The Institute needs some level of intellectual or scientific expertise from the partner to justify the agreement. He also explained that a Government employee may not have equity in a CRADA partner; if a Government invention is part of a CRADA transaction, the inventor can receive the royalties normally paid as part of his compensation from the Government but cannot receive any consulting fee from the CRADA partner. The usual conflict of interest rules apply; however, receipt of royalties is not a conflict of interest.

A question was asked about the possibility that in a CRADA involving clinical trials, the right to publication of results would be given to a private company. Dr. Mays responded that the terms of the CRADA in such cases specifies that there will be no restrictions on publication. In response to a question on whether a CRADA might be used to provide clinical trial data to a company that had developed a drug or device, Dr. Mays replied that the mechanism is most helpful with materials developed by the NCI, since the Institute would have more to contribute. Dr. Broder clarified that taxol was discovered by NCI staff and grantees. He added that another important mechanism for transferring technologies is the Small Business Innovative Research (SBIR) program, through which commercial organizations can qualify for research grants or contracts. He noted that the SBIR program constitutes about 1 percent of the budget. Asked whether any data exist on the success of the SBIR program, Dr. Broder suggested putting a report on the SBIR program on the agenda for a future NCAB meeting.

XII. PROGRESS IN INTERNATIONAL COLLABORATION AND INFORMATION DISSEMINATION—DR. FEDERICO WELSCH

Dr. Broder opened this presentation by explaining that the mandate to disseminate information around the world is actually written into the authorities of the NCI Director; he added that this special authority is taken very seriously. The primary barrier to providing access to computerized data in foreign countries is the cost of connecting to the host computer through satellite or telephone hookups. An experimental program designed to address this problem is the compact disk-read only memory (CD-ROM) system, which Dr. Broder described as the most cost-effective information system that the NCI has ever undertaken. He introduced Dr. Federico

Welsch, who heads the Office of International Affairs (OIA), to provide a summary of the total international program, including the CD-ROM project.

Dr. Welsch explained that the OIA is located in the Office of the Director, NCI, and maintains several programs, including short-term and long-term scientist exchanges; oncology faculty development programs in Latin America and the Caribbean, and Central and Eastern Europe; scientific workshops, mostly with Japan; and relationships with multinational organizations such as the International Agency for Research on Cancer, the European Organization of Cancer Institutes, the Pan American Health Organization, and the International Union Against Cancer.

The NCI spends about $25 million a year on international activities, including foreign grants and contracts, the NIH visiting program, bilateral scientist exchanges, and international cancer information dissemination. Dr. Welsch presented slides with information on the numbers of individuals involved in exchanges, countries involved in bilateral agreements, and workshops held. In fiscal year (FY) 1990, 630 scientists joined NCI intramural laboratories under the NIH visiting program. OIA-cosponsored workshops have increased from 16 per year in 1988 to 21 in 1990. OIA-cosponsored scientist exchanges increased from 58 to 112 during the same period.

Dr. Welsch noted, as Dr. Broder mentioned earlier, that the CD-ROM program is being used to distribute copies of CANCERLIT (a bibliographic database) and PDQ (a database with information on tumor types, prognoses, treatments, protocols, and directories of physicians and facilities) to centers in other countries, including Eastern European countries; he provided data on the usage of NCI databases via CD-ROM in Hungary, Poland, and the U.S.S.R. Some of the same information can also be provided through electronic mail or the new Cancer Fax service. The NCI is also making the *Journal of the National Cancer Institute* available free of charge to 217 institutions in the developing world.

Dr. Welsch continued by noting that, under Mr. Paul Van Nevel, Associate Director, Office of Cancer Communications, the NCI maintains a series of Cancer Information Services (CIS) throughout the United States which physicians and patients can call for information. The NCI plans to provide free CD-ROM subscriptions to one additional CIS and to 11 institutions that have large minority enrollment.

Asked about relationships with African countries, Dr. Welsch replied that relationships are developing slowly; Zimbabwe, he said, has accepted a CD-ROM subscription, whereas Kenya and Nigeria have not yet responded. He added that long delays in communication are hampering this effort. Special focus is also being given to Latin America, Eastern Europe, and Asia. In response to another question, Dr. Welsch noted that scientists involved in international exchange through the Fogarty Center are not accounted for in his report.

XIII. SUBCOMMITTEE ON WOMEN'S HEALTH ISSUES— MRS. BARBARA BYNUM

Mrs. Bynum observed that, from this day forward, the NCAB will be expected to participate to an increased level of involvement in matters concerning women and other special populations. In light of this, and considering particularly the new Women's Health Initiative described earlier by Dr. Healy, a proposal is being placed before the Board that a subcommittee be empaneled to address the issue of women's health and that its purview be as described in the statement provided in the members' notebooks. The statement, she continued, represents a sense of what Institute staff and Mrs. Iris Schneider, the Institute's representative to the Office

of Women's Health, believe to be an appropriate indication of the breadth of concerns that would be embraced by such a subcommittee.

Mrs. Bynum asked members to read the statement and consider the need for any modifications, and announced that the subcommittee would be further discussed during the meeting's second day under new business. She also asked any members interested in serving on the subcommittee to speak to her or to Dr. Calabresi.

Secondly, she addressed the issue of the Board's role in follow-up of peer review of applications in situations where the reviewers are asked to consider and comment on the adequacy of inclusion of women and minorities in clinical studies. She said that the NCI is in the final phase of implementing this NIH policy and noted that a copy of the implementation plan is also in the members' notebooks.

She called the attention of members to a sample cover page from a reviewers' summary statement to illustrate a worst case example of an application that reviewers found to lack attention to both gender and minorities; the sample page bears the codes 64 and 74. She noted that the codes on the 60 and 70 series range from applications that are totally appropriate to those found lacking. The 64 and 74 codes are effective bars to funding and require exceptional action on the part of the Institute Director if any funding action is contemplated.

Mrs. Bynum reminded members that, during the closed session, they should note and take appropriate action on any application that remains of concern and for which they require additional information concerning the study section's recommendations regarding women and minorities. The Board can recommend either deferral or approval with consideration of whether or not an exception can be made on the basis of the inclusiveness of the overall portfolio of the given program, or whether some kind of approval can be granted under the condition that the applicant and institution involved be given time to rectify the problem.

To a question on whether the Women's Health Initiative would take the form of a contract or a grant and whether the various advisory boards would be involved, Mrs. Bynum replied that the Directors of the four principal Institutes are expected to take part in the planning of this Initiative; she speculated that all of the contributing Institutes would be involved in identifying possible mechanisms for support. Dr. Greenwald, she added, has drafted a potential program for a comprehensive study to look at three leading causes of death—heart disease, cancer, and osteoporosis—and other Institutes will probably make similar contributions, but specific mechanisms have not been determined.

Dr. Broder stated that Congress is very interested in the capacity of the NIH to make sure that studies embrace the full spectrum of American society, and a legislative movement exists that would affect the focus of various trials. Dr. Broder emphasized the need to show good faith and to achieve these goals without the need for a statutory requirement. The Institute, he continued, will not fund studies with a gender imbalance unless there is a scientific rationale for the imbalance, such as with studies of prostate cancer or breast cancer.

Asked about the gender balance in NCI studies, he stated that the percentage of women in therapy-related trials is about 56 percent. He added, however, that the NCI should not be complacent about this issue.

XIV. OPENING REMARKS, DAY TWO—MRS. BARBARA BYNUM

Mrs. Bynum announced that after discussions with the NIH Office of General Counsel, the Board had been told that it would be permissible to reconvene in open session at a time

earlier than that indicated in the agenda. The following provisos would obtain: one, that the minutes reflect what is being done, and two, that a transcript of these proceedings be made available to any member of the public, or of this Board, who requests it in the future. She added, as a point of further procedural clarification, that members of the President's Cancer Panel and ex-officio members of the Board do not vote; Mrs. Nancy Brinker, however, is still a member of the NCAB as well as the President's Cancer Panel, and thus does have a vote.

XV. SUBCOMMITTEE REPORTS—DR. PAUL CALABRESI

Dr. Calabresi turned the meeting over to Dr. Howard Temin for a report from the AIDS Subcommittee.

AIDS Subcommittee Report

Dr. Temin reported that the AIDS Subcommittee meeting opened with the announcement of a submission by Bristol-Myers/Squibb of a new application for dideoxyinosine (ddI); NCI scientists, including Dr. Broder, played an important role in the development of this drug. No new toxicities have been found since the Phase I trials.

Drs. Yarchoan and Streicher discussed new concepts in basic and clinical investigations of Kaposi's sarcoma (KS). There are several therapeutic directions that can be addressed; however, none of these have produced significant prolongation of survival. Dr. Streicher discussed KS as a tumor driven by angiogenic factors; the AIDS KS cell produces numerous growth factors that induce autocrine stimulation.

Finally, the issue was raised of redefining the NCI's AIDS research in a fashion similar to that used by National Institute of Allergy and Infectious Diseases (NIAID) to identify all efforts related to cancer and to distinguish AIDS cancer research from AIDS retroviral or AIDS epidemiological research, and to indicate when research is related to both AIDS and cancer.

The report of the AIDS Subcommittee was accepted by a unanimous voice vote.

Planning and Budget Subcommittee

Dr. Bernard Fisher presented the report of the Planning and Budget Subcommittee. At this meeting, Dr. Broder presented the NCI's 1993 bypass budget and reminded members that their input from the last meeting had been factored into its development. He then presented the major program assumptions used to develop this budget request; the basic tenet is to restabilize those mechanisms that have shown significant declines in 1980 constant dollars. Basic research through research project grants remains the highest single commitment. Support for intramural research will continue for high-priority basic research and clinical investigations in cancer and AIDS. He also emphasized that the NCI will be seeking funds from the NIH Director as part of the Women's Health Initiative.

There were discussions of the NCI's proposed use of the P50 Centers mechanism for the Specialized Centers of Research Excellence and how they would differ from the P01 mechanisms. These awards were envisioned for initiatives in breast and prostate cancer and would encompass a major commitment to these diseases.

The 1993 bypass budget is currently at $2.745 billion, an increase of approximately $935 million over the 1992 President's request. Dr. Broder emphasized in his report to the Subcommittee that this is a needs budget developed on scientific principles and opportunities.

Slides and other information presented by Dr. Broder will be attached to the minutes of the Subcommittee's meeting. The Subcommittee voted to support the bypass budget assumptions.

Mrs. Brinker suggested that a more comprehensive approach was needed in presenting the National Cancer Program rather than allowing the Congress or the public to be swayed by groups with narrow cancer interests. There was some discussion as to how this should be carried out. Dr. Temin mentioned that the Institute of Medicine had developed a research agenda and funding recommendations for the National Institute on Aging, and suggested that something similar could be done for the NCI.

Ms. Whalen presented results of a pilot evaluation of the Outstanding Investigator Grant (OIG), developed with the NCI's OIG Working Group and Executive Committee. Data were from the first cohort of OIG recipients who received the grants in 1985 and the study was a descriptive one. Questions focused on whether the OIG provided flexibility for grantees to initiate innovative or high-risk projects, whether the research supported was cancer-relevant, whether the OIG relieved the grant-related administrative burden, and whether the mechanism affected the scientific output of the grantee. Dr. Temin suggested that if an impact evaluation is eventually done for the OIG, it might be worthwhile to simultaneously evaluate the MERIT awards.

Mrs. Bynum presented the latest version of the OIG guidelines and highlighted changes, which will be described in the minutes of the Subcommittee meeting. In addition, Mrs. Bynum said that proposals are being developed to move from a mail ballot to committee review of OIG applications.

The report of the Planning and Budget Subcommittee was accepted by a unanimous voice vote.

Cancer Centers Subcommittee

Dr. Durant reported that the Cancer Centers Subcommittee received a review of what had happened to applications for comprehensive status. Eleven institutions were considered at the time of the core grant reapplication through peer review and five core grant reapplications were considered administratively. All 16 were approved for comprehensive status. A question arose concerning the definition of a consortial Center, at least two of which are funded. It was suggested that perhaps the last four of the current comprehensiveness criteria would apply to the consortial Centers.

The Subcommittee discussed a proposal to create Regional Enhancement Cancer Centers; the notion is that Centers in States that do not have Cancer Centers would be able to apply for "mini" core grants if they developed a formal collaboration with an NCI-designated Comprehensive Cancer Center in another State. This concept will go forward through the Board of Scientific Counselors. There is also a plan to seek planning grants from certain institutions, which will also go before the Board of Scientific Counselors.

A lengthy discussion focused on the financial issue of putting caps on Cancer Centers. Dr. Durant said the budget for Centers has been relatively flat in actual dollars for some years. The growth of some of the early Centers may inhibit the ability to create new Centers. Proposals have been made to place a cap on the size of an institution's core grant; one suggestion was to use a sliding cap based on the age of the center and the size of its grant. Another idea related to size of the "apple" in comparison with the "core." It is easy to determine the total research base supported by the NCI, but more difficult to determine the extent of all the other peer-reviewed

support received by the Center. Another proposal was to relate the largest grant available to the total Center's budget; no one was in favor of pursuing that idea further.

The report of the Cancer Centers Subcommittee was accepted by unanimous voice vote.

Subcommittee on Information and Cancer Control for the Year 2000

Dr. Bettinghaus reminded members that concepts from this Subcommittee are presented to the NCAB for approval, since the Office of Cancer Communications does not have its own Board of Scientific Counselors. He said there were three concepts to be presented; acceptance of the Subcommittee's report would indicate acceptance of these concepts.

Dr. Bettinghaus noted that the telephone information service provided by the NCI's Cancer Information Service has grown over the years, and that approximately half a million calls a year are being received from the public. Under the system's current load, about 58 percent of the time a caller receives a busy signal. The contracts for this service come up for renewal at the end of 1992, and it is proposed that the way in which the CIS is operated be changed, not in terms of what it does, but in terms of how it tries to cover the entire country.

Presently, individuals bid for a CIS contract by responding to an RFP; after peer review a specific number of contracts are awarded. This leaves the CIS without the ability to guarantee coverage of the entire United States, and there have been areas left without a local or regional service. A national contract has served as a fallback for these areas. The new proposal is to set up a series of regions designed to cover the entire country, and take bids by region. A super office will be located in one of the regions, probably located in the Midwest or on the west coast, to provide evening service, which is more hours of coverage than most regional offices. The proposed budget provides for an eventual 20 percent increase in phone service, through adding WATS lines and additional staff, to reduce the percentage of busy signals. Before the RFP is introduced, there will be a meeting of current contractors and other interested parties in June to provide them with information on the regional system.

The other program areas, in addition to the telephone service, are resource development and outreach. The outreach function will specifically mandate assistance in regions to reach groups that are currently not being reached by the telephone service.

The maximum CIS budget proposed for FY 1993 is $16.1 million, compared with $10.4 million in FY 1992; in all probability, Dr. Bettinghaus added, the Director's Office will not be able to provide this maximum funding. It has also been proposed that funding be planned on a 10-year basis, with an original five years of funding established and reviewed for renewal.

The second proposal is for the Public Inquiries Section, another area within the Office of Cancer Communications (OCC), for the Technical Writing and Publications Distribution Service. The OCC is responsible for answering approximately 370,000 cancer information requests each year for the NCI, Congress, or other government agencies and for writing educational materials. All letters are answered with individual letters or publications distributed through a warehouse. The proposal would support a five-year contract that has existed since 1974 for approximately $13 million over the entire five years.

The third concept is for two new SBIR contracts. One would be for the development of a portable device for storing a cancer patient's individual medical history. The second would support the development of a computer workstation that the user could talk to to obtain information from PDQ, in essence creating a public-oriented PDQ service. The SBIR contracts

are a maximum of $50,000 a year for two to three years; this proposal involves a maximum of $250,000 a year for both of these research projects.

Asked how many CIS services are operating without funding, Dr. Bettinghaus stated that five approved centers are operating without funding. Part of the purpose of the planned June workshop is to see what kind of proposals and suggestions those services will have under a regional system.

Another question related to the possibility of collaboration between the CIS and the information services provided by the American Cancer Society (ACS). Dr. Bettinghaus said that although he has thought for years that this should happen, the ACS has made it unlikely by deciding that their service will no longer provide any kind of treatment information, whereas the CIS is committed to providing such information. Mr. Van Nevel added that the ACS system differs from the CIS system in that it depends on a computerized database for answering questions on local resources and does not emphasize counseling. The two systems are complementary and refer many calls to each other. Dr. Bettinghaus noted that the CIS uses PDQ in answering about 44,000 inquiries a year.

A question was raised concerning whether the regional approach to the CIS would be detrimental to any resources or capabilities that have been set up by current contractors such as local tumor registries or tie-ins with other programs. Dr. Bettinghaus acknowledged this concern and suggested that the existence of such relationships be taken into consideration when setting up the regions.

Mrs. Brinker expressed her appreciation and support for the work done by the CIS and the OCC.

Considering the expense of developing new computer applications like the voice recognition computer and providing public access to it, a member brought up the idea of using a 900 telephone number instead of an 800 number to offset the increasing cost of providing this information service, and asked whether the CD-ROM system and the use of regional offices are expected to lead to any cost savings. Dr. Bettinghaus said that this idea has been discussed; while it is not imagined as the basis for the CIS itself, the use of a 900 number has been suggested for some systems as a test.

He added a comment about the concept of voice recognition, observing that it would not be an easy task to develop such a system, since it would be particularly difficult to develop a system that could recognize a wide variety of voices. He expressed hope that computer experts would be included among the reviewers for these applications. Ms. Susan Hubbard offered an additional comment about the voice recognition computer. She said that the SBIR contract would be a feasibility study and that if nothing was produced that was considered to be worthwhile by peer reviewers, the idea could be dropped. In terms of the effect of the CD-ROM on costs, she added that this system is expected to save the CIS at least $250,000 a year in on-line computer costs. As CD-ROM is introduced into more hospitals and libraries, she continued, the costs of accessing information for many health professionals will be reduced.

Concerning the issue of a 900 number, Dr. Bettinghaus said that one question that needs to be asked is to what extent the NCI is required under its funding to provide information services and to what extent it ought to be able to charge for information. Mr. Van Nevel noted that a 900 service might reduce the utilization of the service by persons of lower socioeconomic status. One idea that has been suggested is to use new advances in technology such as the new AT&T FTS2000 system to use the 800 number as a gateway to a 900 line for selected information services. For example, a physician seeking access to PDQ could call the 800

number and be shunted to the 900 line, while callers seeking basic cancer information could remain in the 800 system. Dr. Broder added that an agency cannot charge a fee for a service without the proper legal authority.

Concerning the ability of the NCI to recover funds from providing information on CD-ROM, Ms. Hubbard stated that some limited royalties—between $60,000 and $90,000 a year—were received based on the cost of the product. Dr. Broder added that these funds were placed in an account at NTIS to support other information dissemination activities. For example, these funds pay for the distribution by NTIS of a new PDQ user guide.

A question was asked on the demographics of CIS users. The reply was that the CIS is allowed to collect data on 20 percent of its users, which probably does not adequately represent all callers because of variations in promotions. It takes about six months to analyze the data. Current figures indicate that 70 percent of CIS users are women; 89 percent are White, 2 or 3 percent Black, 2 percent Hispanic, and the remainder other or unidentified. The Community Outreach Program is being restructured to specifically target underrepresented populations. Dr. Bettinghaus said that a series of studies has been proposed to investigate the effects of outcalling—the use of coordinators to contact minority groups in targeted areas to try to increase usage of the service.

In terms of cooperation between the various types of cancer information services, Dr. Bettinghaus stated that there is considerable contact between the CIS and the ACS; he noted, however, that there is a question of whether the NCI can support the efforts of local hospitals to use the information service to attract patients to the hospitals.

To a question on whether the SBIRs are limited to small businesses, Ms. Hubbard replied that large businesses can also apply. Mrs. Bynum clarified this by noting that the cognizant offerer must be a small business, though it can be part of an alliance with a larger business.

A member asked whether any studies had been done to determine the outcome of information services provided through the CIS—whether people follow up on the information they receive. Dr. Bettinghaus said that an RFP had been issued several years ago on this subject and several studies were still in the field. He expressed the opinion that the RFP should be reissued. Mr. Van Nevel suggested research on cancer communications as an appropriate area for investigator-initiated studies. Ms. Hubbard noted that the Agency for Health Care Policy Research had issued an RFA recently to evaluate the effectiveness of tools such as the CIS and PDQ.

The report of the Subcommittee on Information and Cancer Control for the Year 2000 was accepted by a unanimous voice vote.

Subcommittee on Minority Health Professional Development

Dr. Calabresi announced that the report of the Subcommittee on Minority Health Professional Development could not be presented due to an emergency that called away the Subcommittee Chair, Dr. Kenneth Olden. However, Dr. Calabresi offered to present the gist of the meeting and then turn the floor over to Dr. Vincent Cairoli, who was at the meeting. The minutes of the Subcommittee meeting will be distributed and voted on by mail.

Two issues were discussed. The first involved strategies to improve recruitment of health professionals and the second concerned the need for the Subcommittee to expand its mission by going back to its original focus on minority health in general in addition to its current

focus. It has been proposed that the name of the Subcommittee be changed to the Subcommittee on Minority Health and Professional Development. Dr. Cairoli added that the Subcommittee felt that baseline data should be collected to get a better idea of the mechanisms available for training minority students. He noted that this topic would be on the agenda of the December NCAB meeting under the title "Overview of Minority Programs."

The marketing subject also came up again, he added. It was suggested that existing programs are simply not sufficiently well known. Another question was the status of minority students at majority schools. Dr. Lemuel Evans promised to provide more up-to-date information on that. Dr. Olden felt that it was important to hear from minority students as to the problems instead of relying only on the schools. Finally, the fourth task suggested was that the Subcommittee investigate mechanisms for identifying the top minority students graduating from high school to establish mentor relationships for them at participating colleges and universities.

Dr. Calabresi suggested that Dr. Cairoli had made a comprehensive enough report on the meeting and asked the Board to approve the report; the report was approved by unanimous voice vote. Dr. Calabresi repeated that the minutes would be distributed by mail.

XVI. NEW BUSINESS—DR. PAUL CALABRESI

Dr. Calabresi announced that the Subcommittee on Activities and Agenda, the Working Group, would meet in July. He suggested that the Working Group might consider reorganizing the NCAB meetings so that closed sessions are held in the first afternoon of the meeting, with subcommittee meetings following. Dr. Salmon supported this idea and added that interested individuals who wanted to attend the subcommittee meetings would have to be notified. Mrs. Bynum stressed the fact that public notice must be given of all meetings, whether of subcommittees or the full Board. She added that the possibility exists of holding subcommittees on Sundays or as working lunches. She said the Board ought to consider trying to have meetings at times during which the largest number of members can be in attendance.

Dr. Calabresi repeated that this issue will be taken up at the July subcommittee meeting. He then raised the first item of new business, the empaneling of a new Subcommittee on Women's Health. Hearing no questions or comments, he empaneled the Subcommittee, but stated that he would not appoint any members at this time because time had been promised for members to indicate their interest. Mrs. Bynum noted that she had received notes from several members expressing interest. Dr. Calabresi said that he would look over the names and perhaps wait until the final appointments to the NCAB have been made.

He then made the Board aware of his interest in forming a new Subcommittee on Cancer and Aging. He said that he had had informal discussions with Dr. Broder and with Dr. Frank Williams, who is head of the National Institute on Aging, who both expressed interest in having a collaborative program.

Dr. Calabresi called the members' attention to a function statement on the Subcommittee on Clinical Investigations in their notebooks under "New Business." He reminded the members that this is an expansion of the Surgical Oncology Subcommittee. Dr. Wells will remain as Chairman and the membership will also remain the same.

Dr. Calabresi then asked for any suggestions for future agenda items. Dr. Salmon stated that he would like to follow up on Dr. Broder's comments from yesterday on P01 grants. He suggested a discussion for the next meeting on the idea of giving priority to P01s that involve translation of laboratory information to the clinic, with the view that there is not a working system of R01s for that purpose. Dr. Broder agreed with the spirit of Dr. Salmon's comments,

and stated that anything the Board could do to advise the Institute as to the best way to manage the portfolio would be very welcome. He agreed that the P01 mechanism is an excellent one for doing lab to clinic transitions, and said that is why it is used by the NCI more than by the average Institute.

Dr. Salmon suggested a resolution recommending that the NCI's P01s be counted as grants based on the individual projects incorporated. During the discussion that followed, Dr. Broder explained that the current target for new and competing grants was formulated based on the current mix of P01s and R01s in the portfolio; he argued that if the average cost of a research project grant was changed by counting the projects within a P01 as grants, the target thresholds would be recalculated in proportion, and no advantage would be gained. It would not be considered fair play, he argued, to start counting grants that had never been counted before. He suggested that an alternative would be to urge that more flexibility be accorded to the NCI in making a good faith effort to reach its target goals and place a higher priority on funding certain project grants because of its historical commitment to P01s.

Dr. Calabresi asked whether Dr. Salmon's resolution could be rephrased to be most helpful. Dr. Salmon moved that the NCI be given sufficient flexibility in its grant target to permit the funding of those P01s that, in the Institute's judgment, are the most valuable way to promote the laboratory/clinic interface in cancer research. The motion was seconded and then approved by a unanimous voice vote.

Mrs. Brinker offered a resolution commending and congratulating the M. D. Anderson Cancer Center at the University of Texas as that institution celebrates its golden jubilee and expressing appreciation for its major and far-reaching contributions to cancer research and cancer control. Mrs. Brinker's motion was passed unanimously.

The Board then voted unanimously to approve the minutes of the February 1991 NCAB meeting.

Dr. Durant asked for an opportunity to follow up on the discussion of yesterday on scientific integrity. He suggested a recommendation from the Board to the DHHS that a statute of limitations of seven years be applied to the investigation of scientific misconduct. Dr. Broder suggested an exception in cases involving the abuse of human subjects, with which several members expressed agreement. This motion was approved unanimously. Dr. Durant offered a second motion that the Board encourage the OSI to publish data regarding the outcome of its investigations to make the dimensions of the problem clearer. The motion was modified to include a timeline of one year for the production of the report and a suggestion that such a report be produced annually. As modified, the motion was approved unanimously.

Mrs. Bynum offered two information items. There will be a mail ballot in August for two applications requesting support for the proton beam facilities. The second item is a change in terminology: the individuals who previously have been designated as Executive Secretaries will be known from this time forward as Scientific Review Administrators, or SRAs.

Dr. Jako asked what had happened to the NCI logo. It was explained that the logo Dr. Jako referred to could still be used as the official seal of the Institute but is now rarely used. Dr. Jako also asked whether activities were planned to commemorate the 20th anniversary of the National Cancer Program. Dr. Broder said that some low-key ceremonials were being planned,

including several arranged by private organizations, and that a meeting of the President's Cancer Panel probably would be held at about that time if the Chair concurs. He said that Board members would be kept informed as plans for observations are completed. The possibility was also raised of producing a brochure or other document on the accomplishments of the National Cancer Program and expressing a recommitment to its goals.

August 27, 1991
Date

Paul Calabresi, M.D.
Dr. Paul Calabresi, Chairman